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USUAL AND UNUSUAL REACTIONS TO PROTEIN
(FEVER) THERAPY*

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Shortly after Wright and others introduced specific vaccine therapy about twenty years ago, nonspecific vaccine therapy was introduced. This was soon followed by nonspecific protein therapy. Typhoid vaccine was first used intravenously by Kraus and Mazza¹ in Argentina about 1912. Its use as a preventive of typhoid fever was first advocated by Ichikawa² (1912), and it was first given intravenously as a nonspecific protein for "fever" therapy by Miller and Lusk³ in 1916 in the treatment for chronic infectious arthritis. It has since become one of the most widely used agents for protein or "fever" therapy, is employed for many diseases, particularly of the joints, skin and eyes, and as a substitute for malarial treatment in late syphilis. Recently it has been successfully used in the treatment for occlusive vascular disease⁴ and for evaluating, by means of the "vasomotor index" of Brown, the possibilities of sympathetic ganglionectomy for arthritis⁵ and certain vascular conditions⁶.

* Submitted for publication, March 2, 1931

* From the Division of Medicine, the Mayo Clinic

* Read before the Section on Pharmacology and Therapeutics at the Eighty-First Annual Session of the American Medical Association, Detroit, June 27, 1930

1 Kraus, R, and Mazza, S. Zur Frage der Vakzinetherapie des Typhus abdominalis, *Deutsche med Wchnschr* **2** 1556, 19142 Ichikawa, Sadakichi. Abortubehandlung von typhösen Krankheiten, *Ztschr f Immunitätsforsch u exper Therap* **23** 32 (Sept 5) 19153 Miller, J L, and Lusk, F B. The Treatment of Arthritis by the Intravenous Injection of Foreign Protein, *J A M A* **66** 1756 (June 3) 1916, The Use of Foreign Protein in the Treatment of Arthritis, *ibid* **67** 2010 (Dec 30) 19164 Allen, A W, and Smithwick, R H. Use of Foreign Protein in the Treatment of Peripheral Vascular Diseases, *J A M A* **91** 1161 (Oct 20) 1928. Brown, G E. Treatment of Peripheral Vascular Disturbances of Extremities, *J A M A* **87** 379 (Aug 7) 1926. Brown, G E, Allen, E V, and Mahorner, H R. Thrombo-Angitis Obliterans. Clinical, Physiologic and Pathologic Studies, Philadelphia, W B Saunders Company, 1928. Goodman, Charles, and Gottesman, Julius. Pain and its Treatment in Thrombo-Angitis Obliterans, *New York M J* **117** 774 (June 20) 19235 Hench, P S, Henderson, M S, Rowntree, L G, and Adson, A W. The Treatment of Chronic "Infectious" Arthritis by Sympathetic Ganglionectomy and Trunk Resection, *J Lab & Clin Med* **15** 1247 (Aug) 19306 Adson, A W, and Brown, G E. Treatment of Raynaud's Disease by Resection of Upper Thoracic and Lumbar Sympathetic Ganglia and Trunks, *Surg. Gynec Obst* **48** 577 (May) 1929

TYPE OF VACCINE AND DOSAGE USED

Many thousands of injections of typhoid vaccine have been given at the Mayo Clinic for the treatment in various conditions, generally supplementary to other treatment. For this report a special group of patients on the arthritis service and on the vascular service of Dr. George Brown was studied in the course of the last five years, the number of which was about 2,500. Of these, approximately 1,500 had arthritis, the remainder suffered from various conditions, chiefly vascular diseases. The number of reactions studied was about 10,000.

Various factors influence the reaction: the kind and degree of the patient's illness, the method of administration, type and freshness of the vaccine, the size of the dose, and the response of the patient. Reactions to typhoid vaccine are basically the same as reactions to other foreign proteins. When the substance is given intramuscularly, reactions are minimized and delayed. When it is given intravenously, reactions are sharper, more prompt. The ability to produce fever and other phases of the reaction vary also with different preparations of vaccine. Fresh vaccine gives a more prompt reaction than old vaccine and should be used in smaller doses. Preparations of milk or sulphur are used less frequently at the clinic. Typhoid vaccines made by state boards of health, the United States Army and commercial houses have been used. On the arthritic and vascular services one commercial preparation has been used more than others because of familiarity with the type of reaction from a given dose. This brand is one of the so-called triple-typhoid preparations made from *Eberthella typhi*, *Salmonella paratyphi* and *Salmonella schotmuelleri* or, in more familiar terms, typhoid and paratyphoid A and B. It probably has no particular merit or demerit, however. It is generally given intravenously, occasionally intramuscularly. No set schedule of time or dosage is used. Some advise the administration of foreign protein not oftener than once a week, others (Cowie), every second day. When well borne, at the clinic it is given approximately twice a week. The initial dose is usually from 15,000,000 to 25,000,000 bacilli, subsequent doses are 50,000,000, 75,000,000 or 100,000,000, and so on.⁷

Experience suggests that injections in cases of arthritis usually should be discontinued after from six to ten doses, this does not necessarily hold when patients with vascular disease are being treated. There should be an intermission of several weeks to prevent marked loss of weight ("proteaginous cachexia"), to permit the return of normal equilibrium and restoration of the patient's morale, and because

⁷ The estimation of the number of bacilli in each dose is, of course, only approximate. Although it would be more accurate to state dosage in terms of cubic centimeters of bacterial suspension, the doses are given as they are for comparison and in line with the custom of the majority of previous writers.

further injections frequently prove ineffective. In arthritis, when three or four intravenously administered doses, with moderate reactions, fail to produce definite relief, or if such doses produce increased disability of the joints, the treatment is discontinued in favor of more conservative (intramuscular) protein therapy or treatment with stock vaccines.

THE USUAL REACTION

Although reactions to the intravenous use of typhoid vaccine and other foreign proteins may at times seem severe to the patient, they appear relatively simple to the physician, they usually consist merely of the common clinical phenomena of chill, fever, mild headache, general malaise, mild gastro-intestinal upset, and so on. Further analysis of the reaction, however, shows more than just an "onset by chill and

TABLE 1—*The More Obvious Reaction to Protein Therapy*

	Prodromal Phase Including (a) Latent or Prechill and (b) Chill Period	First "Negative" Phase to Height of Fever, 3 to 5 Hr After Injection	Second "Positive" Phase, Period of Falling Temperature Variable, 6 to 24 Hr After Injection	Subsequent Day
Temperature	No increase	Rising	Falling	Occasionally a secondary rise
Chill	Minor or distinct	Generally absent		Occasionally a secondary chill
Pain, inflammation, swelling, disability, nervous irritability	Usually absent, may be slight	Increasing	Decreased or absent, euphoria	Variable duration of euphoria

fire," and that marked disturbances in the physical and chemical processes of the body are included.

The general nature of the usual reactions has been extensively studied. It manifests itself as a prodromal phase and in two further phases a "negative" and a "positive" phase, generally considered to be distinct (table 1). The period just after the injection is given, and before the temperature begins to rise, is the prodromal phase, consisting of what may be called a prechill and a chill period. Then there begins the first or negative phase, that period from the onset of the rising temperature to the point of maximal temperature. The second or positive phase extends from the height of the fever to the return of normal temperature. Occasionally a secondary chill and fever occur the following day. During the negative or first phase there are inaugurated certain phenomena, some of which seem deleterious to the patient's well-being and which, if long continued, would militate against the usefulness of the treatment. There is in general, however, a sharp reversal of these phenomena at the beginning of the positive or second phase, and during this reversal the processes of healing are markedly

stimulated Innumerable attempts have been made to eliminate or shorten the negative phase by using various vaccines, different proteins or protein fractions and different methods of administration It is generally believed, however, that to obtain a therapeutically positive second phase, there must be an appreciable first phase, and that without the lytic phenomena of the first phase, the healing process which results from stimulation of the defensive mechanism of the body will not be adequate (Donath,⁸ Garrison,⁹ Maliwa,¹⁰ Miller¹¹)

The clinical alterations noted in table 1 constitute the more obvious part of the reaction to foreign protein Further analysis of the reaction in patients and in animals reveals innumerable marked physical and chemical alterations that demonstrate the intensity of the activation of cellular and humoral defenses Complete details concerning alterations in the organic activity of all bodily structures cannot be given here The changes in organic activity are, in general, initiated about the time of the period of chill, and are altered in one direction (increased or decreased) during the first or negative phase, and in the opposite direction during the second or positive phase The reported changes consist of the following (1) alterations in the basal metabolism, (2) peripheral and splanchnic vasomotor changes, including changes in blood pressure and in the caliber and permeability of the arterioles and capillaries, (3) alterations in renal function detectable in the output and acidity of the urine, excretion of phenolsulphonphthalein, and concentration of nitrogen, phosphate, urea, uric acid, allantoin and albumin, (4) alterations in serum ferments, anti-ferments, antibodies and the Wassermann reaction, (5) alterations in organic activity demonstrated by increased secretion of lymph, bile, saliva, breast milk and menstrual flow, and by changes in the activity of the liver, gastro-intestinal tract and spleen, (6) alterations in the volume, specific gravity, freezing point and viscosity of the blood, (7) alterations in the cellular elements of the blood, (8) alterations in the fragility of the blood platelets and in fibrinogen, thrombokinas, coagulation time and sedimentation rate, (9) alterations in the chemical constituents of the blood, demonstrated by the carbon dioxide tension of the plasma, carbon dioxide-combining power, total nonprotein nitrogen of whole blood and of

8 Donath Julius Ueber Herdreaktionen und ihre therapeutisch Bedeutung, Wien klin Wchnschr **40** 9 (Aug 18) 1927

9 Garrison, F H Protein Stimulation (Local Death) and Protein Therapy, Bull New York Acad Med **3** 555 (Sept-Oct) 1927

10 Maliwa, E Kritisches zur Reizkorpertherapie, Ztschr f wissensch Baderk **3** 467 (Feb) 1929

11 Miller, J L The Nonspecific Character of Vaccine Therapy, J A M A **69** 765 (Sept 8) 1917, Non-Specific Therapy, Medicine **6** 513 (Dec) 1927, Biologic Therapy, J A M A **76** 308 (Jan 29) 1921

serum, sugar tolerance, albumin-globulin ratio and concentration of urea, uric acid, sugar, fat, total serum protein and chlorides

Some of the alterations are very slight, temporary and perhaps clinically insignificant. Others are marked and significant from the standpoint of both usual and unusual reactions, and to them are ascribed the successes, negative results and also, probably, the mishaps of protein therapy. The increasing use of protein therapy attests to the belief that although negative results are common, satisfactory, even brilliant, results are many times obtained and mishaps are rare.

Experimental Data—The amazing complexity of the reaction could be more simply understood if it were demonstrated that all changes were initiated through a central mechanism. That the changes are initiated through the sympathetic nervous system was suggested, among others, by Vaughan¹² and by Gellhorn¹³. Petersen and Muller¹⁴ and Petersen, Muller and Boikan¹⁵ have made a most interesting effort to correlate the various alterations and to demonstrate their coordinated activity. They concluded that when live or dead bacteria, or proteins, are injected intravenously, the injected material is removed from the blood stream by the cells of the reticulo-endothelial system and there "fixed". There is first a fixation (prolonged stimulation) of the splanchnic organs (liver, gastro-intestinal tract and spleen especially) in a state of increased organic activity, and of the splanchnic blood vessels in a state of dilatation. At the same time there is a compensatory, opposite orientation or "fixation" in the activity of peripheral organs and vessels. This is demonstrated by depression in the metabolic activity of skin and muscles and constriction in the peripheral blood vessels. Complete reversal of this state later occurs in both the splanchnic and the peripheral regions, and then there is a return to normal equilibrium. If the injections are given continuously, or if they are repeated beyond the point of tolerance, the repeated stimulation leads to the death of cells.

If the reaction in human beings is similarly motivated and expressed, particularly the vascular and vasomotor changes, certain features of the unusual reactions here reported seem more explicable.

12 Vaughan, V. C. Protein Split Product in Relation to Immunity and Disease, Philadelphia, Lea & Febiger, 1913, Poisonous Proteins, J. Lab. & Clin. Med. **2** 15 (Oct.) 1916.

13 Gellhorn, George. Milk Injections for Pelvic Infections in Women, New Orleans M. & S. J. **78** 557 (March) 1926, Milk Injections in Gynecology and Obstetrics, J. Indiana M. A. **19** 229 (June) 1926.

14 Petersen, W. F., and Muller, E. F. Splancho-peripheral Balance During Chill and Fever, Arch. Int. Med. **40** 575 (Nov.) 1927.

15 Petersen, W. F., Muller, E. F., and Boikan, William. The Reaction of the Dog to the Continuous Intravenous Injection of B. Coli, J. Infect. Dis. **41** 405, 1927.

THE UNUSUAL REACTION

When one considers the profound response to an injection, unusual and untoward reactions might be expected not infrequently, yet they are rare. Large series are reported with no untoward response, even to high doses. At the clinic in this series of about 10,000 injections in 2,500 cases, unusual clinical phenomena have been observed subsequent to only twenty injections and in only fourteen cases, but in view of the increased usage of protein therapy they seem of sufficient importance to report. It would be unfair to ascribe to vaccine treatment responsibility for every clinical alteration that occurred in the course of its administration. Therefore, I have here reported only those unusual reactions which seemed to be related to the protein or fever therapy by reason of their unexpectedness, the promptness of their onset after an injection, the nature of their clinical expression and their similarity to previous experiences of others. The reports of unusual reactions observed by others have not heretofore been reviewed extensively, are widely scattered and are given with but brief comments.

I shall present, in briefest detail, data concerning reactions which these fourteen patients experienced within a half hour to forty-eight hours after the injection, and I shall briefly comment on the possible causal relationship between the injection and the reaction. I was not looking for these reactions, and lacked appreciation of their significance until their repetition stimulated particular observation as they occurred and an extensive review of the literature.

The cases are not presented in historical sequence, but are grouped according to the reaction.

CASE 1¹⁶—A woman, aged 53, had chronic infectious arthritis. Previous to the administration of typhoid vaccine her heart and lungs appeared to be normal. After the first dose of typhoid vaccine (35,000,000 bacilli), there was a severe chill but no fever. The increase in temperature began the next morning, and rose to 103 F, the following day it rose to 104 F. A precordial murmur appeared, and for four days the fever was of the septic type. Rales were present at the bases of both lungs, especially the left. Roentgenograms gave evidence of a thickened pleura at the base of the left lung, and some fluid. Eight days after the injection the temperature and pulse rate returned to normal and remained normal. On dismissal the precordial rub was diminished, dulness at the base of the left lung persisted. The condition was supposed to have been subacute pleurisy and pericarditis. Eighteen months later, examination of the lungs and heart gave objectively negative evidence.

CASE 2¹⁶—A woman, aged 51, had chronic infectious arthritis. The lungs were normal on examination. The first two injections (25,000,000 and 35,000,000 bacilli, respectively) were followed by moderate reactions, a temperature of 103 F and diminution of pains in the joints. Twelve hours after the third injection (35,000,000 bacilli), while fever was present, a sore throat developed, and the following day there was sharp pain at the base of the left lung on breathing. The tonsils had

16 The recollection of two previous additional cases in which pleurisy and definite pericarditis had occurred immediately subsequent to the injection of vaccine stimulated these special observations.

been removed. Fever continued for nine days, the symptoms and signs were those of subacute basal pleurisy and pharyngitis. Recovery followed.

CASE 3—A man, aged 32, had chronic infectious arthritis. He had been exposed to contagious parotitis two weeks previous to his coming to the clinic, but he had this disease at the age of 22. Following the first four injections (from 15,000,000 to 50,000,000 bacilli) there were marked reactions and definite improvement in the condition of the joints. A few hours after the fifth injection (50,000,000 bacilli) acute soreness of the left parotid region developed. The gland became about 3.5 cm in diameter, there were definite induration and tenderness graded 2, which subsided entirely by the fifth day.

CASE 4—When the patient was 18 years of age, a node in the right groin had enlarged and become suppurative and it had been drained. It had been normal since that time. She was 37 years of age when I saw her. After each of five injections (30,000,000, 40,000,000, 40,000,000, 50,000,000 and 100,000,000 bacilli) there was a moderate general reaction and definite improvement in the condition of the joints, but there was painful swelling of the right inguinal nodes, which did not recur after the cessation of treatment. Six months later there had been no further adenitis, and the condition of the joints was markedly improved.

CASE 5—A man, aged 55, gave no history of ocular trouble. He had chronic infectious arthritis. The vision of each eye was recorded as 6/15. The pupils and reflexes were normal. The patient read well with a plus 3 lens. Exophthalmos measured 22 mm on the right and 21 on the left. Refraction was advised. After the second injection (50,000,000 bacilli) high fever and chills occurred. The next morning there were pain and photophobia in both eyes, with conjunctivitis. The following day the eyes were very painful and acutely inflamed, the cornea of each was hazy, there was congestion of the ocular conjunctiva and definite bilateral inflammatory glaucoma. Tension on palpation was graded +1 in the right eye and +2 in the left. There was no ciliary injection or iritis. Under treatment, improvement resulted, and the eyes were normal four weeks after the injection. Seven months later there was no ocular trouble.

CASE 6—A man, aged 53, who had chronic infectious arthritis, had had twelve attacks of gallbladder colic over a period of forty years, but none for five years. There was no abdominal tenderness, but roentgen examination of the gallbladder indicated cholecystic disease. The patient worked in a mine and had had a chronic cough for twenty years, the cause of which, after roentgen examination, was said to be pneumoconiosis. Examination of the lungs disclosed only some emphysema and harsh breath sounds. After the initial dose of typhoid vaccine (20,000,000 bacilli) there was a moderate reaction, the temperature was 103 F, but became normal in twelve hours. Just after the chill, however, pain similar to the old gallbladder attacks developed, and there was definite tenderness in the right upper abdominal quadrant apparently due to subacute cholecystitis. This continued for two or three days, with a return of fever to 102 F. Ten days later, without more vaccine, subacute asthmatic bronchitis developed which continued a chronic course for two months. One year later it was reported that the patient had not had symptoms of pulmonary trouble since.

CASE 7—Since appendectomy six years previously, a woman who had chronic infectious arthritis had had mild soreness in the right upper abdominal quadrant four or five times a year. Five months previous to admission she had noted the onset of fever and diarrhea with from eight to ten stools a day. For the last three months she had had mild, weekly attacks of soreness in the right upper abdominal quadrant. The diagnosis, made elsewhere, was possibly typhoid fever, with typhoid cholecystitis, and three doses of typhoid vaccine had been given intravenously,

without influence on the abdominal symptoms. The Widal test was negative. The patient was 29 years of age when she came to the clinic. Roentgenograms of the gallbladder at the clinic showed normal excretion of dye but "a small stone or papilloma in the fundus." Half an hour after the first injection there had been a sudden onset of soreness over the region of the gallbladder, which lasted six hours. The right side of the abdomen was tender. Two hours after injection, the gums, at the site where teeth had been extracted four days previously, suddenly became sore. The pain lasted half an hour. There was considerable focal reaction in the joints. On the following day the temperature was 100.5 F. Three days later the second injection (50,000,000 bacilli) was given. There was a moderate, generalized reaction. Two hours after injection there was a sudden recurrence of the pain in the right upper abdominal quadrant. Soreness and tenderness lasted all night, associated with a focal exacerbation in the joints. There was no soreness at the site of the recent dental extraction, but a sudden onset of toothache in the region of a condemned tooth. Operation was advised. Chronic catarrhal cholecystitis, with a papilloma at the fundus of the gallbladder, was found. Typhoid bacilli could not be cultured from the gallbladder. Recovery was uneventful.

CASE 8—For several summers a woman, aged 28 when she came to the clinic, had had short attacks characteristic of acute appendicitis. The last attack had occurred one year previous to admission to the clinic. On admission, for chronic infectious arthritis, there was definite tenderness in the region of McBurney's point. The patient would not consider operation. There was very little systemic reaction to the first three injections of vaccine (25,000,000, 35,000,000 and 35,000,000 bacilli, respectively). After the fourth injection (50,000,000 bacilli) the temperature was 101 F. On the following morning the temperature was also 101 F, and there were chills and vomiting. In the afternoon there was localized abdominal soreness. Operation was performed and appendicitis without peritonitis was found. The report on examination of the removed tissue was that of acute hemorrhagic appendicitis. Recovery was uneventful.

CASE 9—Three months previous to admission for chronic infectious arthritis, a man, aged 40, had had an acute attack of disease of the gallbladder. The gallbladder and appendix were removed. After the first injection (25,000,000 bacilli) there was a slight reaction and the temperature rose to 100 F. Then it became normal. Thirty-six hours after injection the temperature suddenly rose to 101 F. There were severe, general abdominal pain, nausea and vomiting, tenderness over the scar of the operation on the gallbladder, and diarrhea. Abdominal distress continued for three days, then it completely ceased. Apparently the condition was sub-acute enteritis. Two years later it was reported that there had been no abdominal discomfort or diarrhea since the patient's dismissal.

CASE 10—A woman, aged 50, had rheumatic fever which was unresponsive to ordinary treatment, she also had erythema nodosum. She gave no history of previous abdominal trouble. After the first injection (15,000,000 bacilli) there was a febrile reaction and the condition of the joints was much improved. The erythema nodosum commenced to fade. The temperature was occasionally normal throughout the next four days. After the second injection (15,000,000 bacilli) there was a moderate reaction. The following morning the patient felt very well. In the afternoon there was a sudden onset of nausea and vomiting, general abdominal tenderness appeared and became localized in the right lower quadrant. The leukocytes numbered 14,800 per cubic millimeter of blood. Operation disclosed acute diffuse purulent appendicitis and periappendicitis. Recovery was uneventful. One year later the patient was in excellent health.

CASE 11—A woman, aged 59, had arteriosclerotic vascular occlusion affecting the feet. She had had corneal trouble, but it had been inactive for several years.

The first two injections (15,000,000 and 25,000,000 bacilli, respectively) were well borne. The third injection (35,000,000 bacilli) caused right palpebral conjunctivitis. There was no definite iritis. The fourth injection (25,000,000 bacilli) was well borne. After the fifth injection (50,000,000 bacilli) there was a moderate reaction. On the following day, redness of the right eye was seen. This developed into typical dendritic keratitis of the herpetic type. Subsequently, this ceased. After three weeks there was complete healing.

CASE 12—A man, aged 52, had had pains of claudication in the right leg for one year. The femoral and popliteal arteries were pulsating. The large arteries of the feet were occluded. The urine was normal on examination. The concentration of urea in the blood was 34 mg per hundred cubic centimeters. The patient was admitted to the hospital in order that the vasomotor index might be determined. One injection (50,000,000 bacilli) was given. One hour later chills appeared and lasted for twenty-five minutes. That afternoon there was a sudden onset of severe pain from the back of the left leg to the left lumbar region and numbness of the left foot. The femoral pulse was lost. The pain was excruciating and was not controlled by opiates. On the following morning, anuria was present. That night the patient died in spite of efforts to restore renal function. At postmortem examination, advanced arteriosclerosis and thrombosis of the iliac arteries were found. The kidneys were essentially normal.

CASE 13—A man, aged 51, had undergone resection of a malignant papilloma of the stomach five months previous to admission. Recently he had had acute polyarthritis. The urine was normal on examination, the recovery of phenolsulphonphthalein was normal. The concentration of urea in the blood was 17 mg per hundred cubic centimeters. The history was negative for lower intestinal or renal disability. Because of severe chronic infectious arthritis, which was not relieved by ordinary measures, one injection (25,000,000 bacilli) was given. There was a moderate reaction, with a rise in temperature to 100 F, then the temperature became normal. On the following morning there was a secondary rise in temperature. Diarrhea appeared, with diffuse abdominal soreness and slight rigidity, which continued the following day. There was no localization of the abdominal pain. The leukocytes numbered 30,000 per cubic millimeter of blood. The third day after the vaccine had been given, anuria and cessation of diarrhea developed. The concentration of urea in the blood was 116 mg per hundred cubic centimeters. Anuria continued and the concentration of urea in the blood rose to 270 mg per hundred cubic centimeters in spite of repeated intravenous injection of diuretics and the use of hot packs. Bilateral renal capsulotomy and left renal sympathectomy were performed. The following four days, the output of urine increased to 500 cc a day, but the concentration of urea in the blood rose to 236 mg per hundred cubic centimeters. Coma and death supervened. At postmortem examination evidence of acute nephritis or definite arteriosclerotic changes was not found. The anuria was unexplained on the basis of the condition of the renal tissue. Acute ulcerative colitis, acute purulent prostatitis, arteriosclerosis graded 2 and subacute pericarditis were found.

CASE 14—A man, aged 38, presented marked deformities, generalized emaciation and secondary anemia. He had chronic infectious arthritis. Transfusion was performed. The urine was essentially normal on examination. Keratitis developed. Protein therapy was suggested. After the first injection (50,000,000 bacilli) a moderate reaction appeared. Pains in the joints improved. Ten hours later, a sore throat developed. On the following day the temperature was 103 F, and pharyngitis, laryngitis and edema of the epiglottis were present. One week after the injection

tion the condition of the eye was improving, although that of the throat was not. In the urine, the amount of albumin was graded 1, and the number of erythrocytes, 3. Sixteen days after the injection slight bronchitis was present, and twenty-six days after the injection anuria appeared. Anuria continued for three days in spite of treatment. Cardiac failure and death supervened. At postmortem examination, bronchitis, bronchiectasis, abscess and slight empyema were found. Acute diffuse nephritis also was present, but there was no evidence of previous nephritis or of definite arteriosclerotic changes in the kidneys.

Reports by Others—Although the reactions recounted here were diverse, they were, including fatalities, in general comparable to those which have occurred elsewhere after the use of various proteins and which have been reported by a number of clinicians. The reactions that have been reported represent a very small incidence among the enormous number of patients who must have been treated by means of foreign proteins. Particularly noteworthy are the cases reported by Irons,¹⁷ Miller,¹⁸ Schmidt,¹⁹ Petersen,²⁰ Ginsburg,²¹ Allen and Smithwick²² and Richardson.²³

Reactions in arthritic patients after the intravenous administration of typhoid vaccine have been reported as follows: delirium tremens, pneumonia and death of a patient with alcoholism and arthritis (Miller, Scully²⁴), delirium tremens and recovery in four additional such cases (Cecil,²⁵ Miller, Scully), delirium and recovery of a patient with arthritis who did not have alcoholism (Cowie and Calhoun²⁶), vomit-

17 Irons, E. E. The Treatment of Gonococcus Arthritis by Injections of Dead Gonococci, and the Clinical Reaction which Follows the Injections, *Arch Int Med* **1** 443 (May) 1908, The Clinical Use of Foreign Protein, *Tr. A. Am. Physicians* **32** 91, 1917.

18 Miller (footnote 10, first and second references).

19 Schmidt, Rudolf. Zur Frage der Herdreaktionen ihrer Spezifität und ihrer diagnostisch-therapeutischen Bedeutung, *Deutsches Arch. f. klin. Med.* **131** 1 (Dec. 12) 1919, Ueber das Problem der Proteinkörpertherapie, *Med. Klin.* **2** 695 (July 4) 1920.

20 Petersen, W. F. Serum Changes Following Protein "Shock" Therapy, *Arch Int Med* **20** 716 (Nov.) 1917, The Non-Specific Reaction, *J. A. M. A.* **76** 312 (Jan. 29) 1921. Protein Therapy and Nonspecific Resistance, New York, The Macmillan Company, 1922.

21 Ginsburg, I. S. Complications in Protein Therapy, *Vruch. gaz.* **30** 1003 (Oct. 31) 1926.

22 Allen, A. W., and Smithwick, R. H. The Treatment of Vascular Lesions of the Extremities, *J. Michigan M. Soc.* **28** 38 (Jan.) 1929, Thrombosis of Peripheral Arteries Following the Intravenous Injection of Typhoid Vaccine. Report of Two Cases, *New England J. Med.* **200** 217 (Jan. 31) 1929.

23 Richardson, H. E. Personal communication to the author.

24 Scully, F. J. The Reaction after Intravenous Injections of Foreign Protein, *J. A. M. A.* **69** 20 (July 7) 1917.

25 Cecil, R. L. A Report on Forty Cases of Acute Arthritis Treated by the Intravenous Injection of Foreign Protein, *Arch Int Med* **20** 951 (Dec.) 1917.

26 Cowie, D. M., and Calhoun, Henrietta. Nonspecific Therapy in Arthritis and Infections, *Arch Int Med* **23** 69 (Jan.) 1919.

ing, epistaxis and death (Irons), hemiplegia in a case of acute arthritis, with septic endocarditis (Cowie²⁷), cardiac dilatation in a case of acute articular rheumatism with mitral endocarditis (Scully), hematuria (Campbell²⁸), and frequent herpes labialis (Cecil and others) Thomas²⁹ stated, also, that he had heard of several deaths in patients with acute arthritis and serious complications, but details of them are not available

In four cases of arteriosclerotic vascular disease, acute thrombosis has occurred Allen and Smithwick reported femoral thrombosis and popliteal thrombosis, both necessitating amputation Richardson had two fatalities following acute femoral thrombosis

Marked temporary nephritis and exacerbation of cutaneous conditions occurred in dermatologic cases (Engman and McGarry³⁰), hemorrhage into the iris, in a case of tuberculous iritis (Cowie), facial herpes in one case of general paralysis, and acute abscess about a symptomless dental root, associated with mania, in another case (Mackenzie³¹)

A group of observers have reported untoward occurrences after typhoid vaccine had been given intravenously in cases of typhoid fever These have included vasomotor collapse, delirium, psychosis, epistaxis, enteritis and, in eleven cases, death following hemorrhage, usually intestinal (Gay and Chickering,³² Von Adelung,³³ McWilliams,³⁴ Kibler and McBride,³⁵ Fairley,³⁶ Miller)

27 Cowie, D M XVIII Nonspecific Protein Therapy in Arthritis, J A M A **76** 310 (Jan 29) 1921

28 Campbell, A D The Use of Non-Specific Foreign Protein in the Treatment of Inflammatory Lesions in the Female Pelvic Organs, Canad M A J **16** 413 (April) 1926, Non-Specific Therapy in Rheumatoid Arthritis, Glasgow M J **103** 79 (Jan) 1925

29 Thomas, H B Arthritis and Foreign Protein, J A M A **69** 770 (Sept 8) 1917

30 Engman, M F, and McGarry, R A Treatment of Certain Diseases of the Skin, J A M A **67** 1741 (Dec 9) 1916

31 Mackenzie, J M Pyrexia Induced by Intravenous Protein Therapy in General Paralysis, Lancet **2** 223 (July 30) 1927

32 Gay, F P, and Chickering, H T Treatment of Typhoid Fever by Intravenous Injections of Polyvalent Sensitized Typhoid Vaccine Sediment, Arch Int Med **17** 303 (Feb) 1916

33 Von Adelung, Edward Vaccine Treatment of Typhoid, California State J Med **18** 175 (May) 1920

34 McWilliams, Helen I The Treatment of Typhoid Fever with Typhoid Vaccine Administered Intravenously, M Rec **88** 648 (Oct 16) 1915

35 Kibler, C S, and McBride, L F Intravenous Injection of Typhoid Vaccine, J Infect Dis **21** 13 (July) 1927

36 Fairley, K D The Treatment of Typhoid Fever by Intravenous Vaccines, M J Australia **2** 291 (Sept 22) 1923, A Preliminary Report on the Treatment of Typhoid Fever with Intravenous Vaccines, *ibid* **2** 428 (Nov 12) 1921

After the intramuscular and subcutaneous use of typhoid vaccine, acute pleurisy in several cases of pulmonary tuberculosis was noted by Clovis and Mills³⁷ After its use for vaccination there have been reported cases of acute appendicitis that have developed from latent or quiescent appendicitis, focal pulmonary reactions in tuberculosis, bilateral atrophy of the optic nerve, axillary adenitis (five cases), rheumatic purpura, acute diarrhea (ten cases), asthenia, mania, one death from acute

TABLE 2—*Unusual Reactions to Protein Therapy (Other Than Typhoid Vaccine) Reported Elsewhere*

Author	Substance Used	Substance Given for	Reaction
Ginsburg ²¹	Milk	Arthritis	Acute appendicitis (latent)
Schaverin (quoted by Ginsburg) ²¹	Milk	Arthritis	Acute appendicitis (latent)
Irons ¹⁷	Meningococci intravenously	Gonorrheal arthritis	Anuria, death (thrombosis of left renal artery)
Ginsburg ²¹	Milk	"Joint disease"	Adenitis, lymphangitis
Sudler (J A M A 75 176 [July 17] 1920)	Phylacogen	Rheumatism	Death ("anaphylaxis")
Schmidt, DeCourcy ⁵⁴	Milk	Arthritis	Tonsillitis, exacerbation
Kaess (Deutsche Ztschr f Chir 183 316, 1923)	Various	Arthritis	"Bloody diarrhea", enteritis (?)
Laurie (M J Australia 1 309, 1923)	Bacillus coli intravenously	Rheumatoid arthritis	Vasomotor collapse, uremia, death
Lamson (J A M A 82 1091 [April 5] 1924)	Antistaphylococcus serum	Acute rheumatism	Death (thrombophlebitis of iliac veins)
Petersen ²⁰	Various	Arthritis, old cardiac lesion	Cardiac enlargement
McLean (J A M A 60 588 [Feb 22] 1913)	Phylacogen	Articular rheumatism	Circulatory collapse, anuria, death
Schmidt, DeCourcy	Milk		Acute cholecystitis (latent)
Beigelman (California Med 10 404, 1929)	Milk	Uveitis	Secondary glaucoma
Irons ¹⁷	Meningococci intravenously	Typhoid fever	Edema of lung, hemorrhage of brain and eye, death
Hektoen and Irons ⁶⁰	Polyvalent stock vaccine	Thrombophlebitis	Pulmonary embolus
Wood ⁴³	Phylacogen	Pneumonia	Death ("anaphylaxis")
Wood	Phylacogen	Typhoid fever	Death ("anaphylaxis")
Darier ⁵⁰	Milk	Keratitis	Death (cardiovascular depression)
Laufer ⁷¹	Novaprotein	Duodenal ulcer	Severe hemorrhage, cachexia

cardiac dilatation and eight deaths from anaphylaxis. Unusual reactions to proteins other than typhoid vaccine are given in table 2.

In addition, I have found reports written by about thirty different observers of about forty other different reactions occurring after the administration of a variety of substances in a group of patients with diverse complaints. Many were severe focal reactions of the condition primarily under treatment, hence, unusual only in degree. Others were more unusual, appearing in unsuspected sites. They included such reactions as the following: activation of latent and quiescent

³⁷ Clovis, E. E., and Mills, G. E. Effects of Typhoid Fever and Typhoid Vaccine on Pulmonary Tuberculosis, J A M A 74 297 (Jan 31) 1920.

urticaria, asthma, epilepsy, gout and malaria, provocation of bleeding in cases of hemophilia and epistaxis, and of gastric crises in tabes, painful transient splenomegaly, onset of "cloudy vision" in albuminuric retinitis, hematuria in cases of tuberculous kidney, acute furunculosis in cases of diabetes, exacerbation of pain and swelling in tuberculous lymphoma and gonorrheal bubo, perforation of corneal ulcers, other untoward ocular reactions in cases of disease of the eyes,³⁸ activation of old quiescent typhoidal spondylitis and tuberculous spondylitis, exacerbation of various cutaneous lesions such as tuberculids, syphilids, leprosy and others, increased secretion in old fistulas and in cases of gonorrheal infection of the genito-urinary tract, increased bronchiectatic excretion, and focal pulmonary reactions in cases of latent tuberculosis

Sudden deaths generally considered "anaphylactic" have been reported by Darier,³⁹ Shipp,⁴⁰ Russel,⁴¹ Myers,⁴² Wood,⁴³ Thomas,²⁹ Lemoine,⁴⁴ and in the United States Naval Medical Bulletin⁴⁵ It is possible that some of them may have been from acute vasomotor collapse, rather than from true anaphylaxis (Scully²⁴)

In considering the types of unusual reactions seen here, in particular appendicitis, cholecystitis, glaucoma, respiratory infections and ulcerative colitis, it must be realized that for these very conditions protein therapy has been used with impunity, and at times even with success. It has been used for appendicitis by Erdély,⁴⁶ for primary glaucoma by Patton⁴⁷ and by Berneaud,⁴⁸ for secondary glaucoma by Howard,⁴⁹

38 Benedict, W L Protein Therapy in Ophthalmology, Minnesota Med **11** 203 (April) 1928 Tobias, G Focal Reaction in Eye in Protein Therapy, Klin Wchnschr **1** 515 (March 11) 1922

39 Darier, A Pour et contre les injections de lait, Clin opht **25** 607, 1921

40 Shipp, J M, quoted by Russell (footnote 41)

41 Russel, J L Report of Two Deaths from Third Inoculation with Typhoid Paratyphoid Vaccine, Some Observations on Typhoid Inoculations, Kentucky M J **22** 378 (Oct) 1924

42 Myers, W A Theory and Practice of Non-Specific Therapy, J Kansas M Soc **20** 30 (Feb) 1920

43 Wood, F C, quoted by Kross J M Research **43** 29 (Jan) 1922

44 Lemoine, A N, in discussion of Allen, T D Typhoid Vaccine in Ophthalmology, Tr Sect Ophth, A M A, 1925, p 135

45 Division of Preventive Medicine Two Deaths Following Inoculation with B Typhosus Vaccine, U S Nav M Bull **25** 736 (July) 1927

46 Erdely, G Protein Therapy und Appendicitis, Fortschr d Therap **3** 691 (Oct 10) 1927

47 Patton, J M The Pros and Cons of Foreign Protein Injections in Affections of the Eye, J Iowa M Soc **12** 387 (Oct) 1922

48 Berneaud Ueber den Wert der Milchinjektionen bei Augenerkrankungen, Munchen med Wchnschr **1** 1040 (Sept 5) 1919, Milchinjektionen bei Augen-Leiden, Berl klin Wchnschr **1** 887 (Sept 15) 1919

49 Howard, H J Non-Specific Protein Therapy in Eye Inflammations with Special Reference to the Use of Typhoid Vaccine, China M J **41** 395 (May) 1927

for neuroretinitis by Boyd⁵⁰ and others, for influenzal pneumonia by Wells,⁵¹ Roberts and Cary⁵² and by Cowie and Beaven,⁵³ in the presence of albuminuria by DeCourcy,⁵⁴ in gastric and duodenal ulcers by Pribram,⁵⁵ Schmidt⁵⁶ and E F Mueller,⁵⁷ in cholecystitis and gout by Schmidt, and in diabetes by Schmidt and by Fischer and Wichmann-Krause⁵⁸ At the clinic Bergen and I have used protein with safety, at times with definite relief, in cases of arthritis associated with ulcerative colitis

"It becomes clearly evident," then, as Petersen²⁰ wrote, "that the identical reaction may alter an inflammatory focus in seemingly diametrically opposite ways, restitution without suppuration, as well as acceleration of suppuration with absorption following"

Clinical Classification—Clinical expression of these so-called focal or "herd" reactions, has been classified by Schmidt and Petersen under three headings (1) stimulation of inflammatory foci of infectious origin, (2) stimulation of inflammatory foci of noninfectious origin and (3) stimulation of latent diathetic phenomena

Stimulation of inflammatory foci of infectious origin may occur at the site of the active primary inflammation, such as the joints in arthritis, the eye in ocular infections, and so forth It may occur at the site of active subsidiary inflammation, such as was seen in the enteritis that appeared in case 9 and in the exacerbation of dental infection and disease of the gallbladder in case 7 It may occur, also, in latent (inactive) and unsuspected foci Here would be listed the majority of my cases, and the reactions would be illustrated by the adenitis in cases 3 and 4, by the appendicitis in cases 8 and 10, by the cholecystitis in case 6, by the respiratory infections in cases 1 and 2 and by the ocular infections in case 11 In certain fields, particularly in genito-

50 Boyd, William Some Uses of Nonspecific Protein Therapy, *J Lab & Clin Med* **5** 88 (Oct) 1919

51 Wells, C W Intravenous Injections of Foreign Protein in Influenzal Pneumonia, *J A M A* **72** 1813 (June 21) 1919

52 Roberts, Dudley, and Cary, E G Bacterial Protein Injections in Influenzal Pneumonia, *J A M A* **72** 922 (March 29) 1919

53 Cowie, D M, and Beaven, P W Nonspecific Protein Therapy in Influenzal Pneumonia, *J A M A* **72** 1117 (April 19) 1919

54 DeCourcy Carroll Observations in Non-Specific Protein Therapy, *Ohio State M J* **20** 86 (Feb) 1924

55 Pribram, B O Proteintherapie und chirurgische Therapie des Magen- und Duodenalgeschwurs, *Deutsche med Wchnschr* **1** 141 (Jan 23) 1925

56 Schmidt, R Protein Therapy in Digestive Disturbances, *Med Klin* **20** 1678 1924, abstr, *J A M A* **84** 238 (Jan 17) 1925

57 Mueller, E F Non-Specific Protein Therapy, Its Action and Its Application, *Wisconsin M J* **26** 287 (June) 1927

58 Fischer Anton, and Wichmann-Krause Stoffwechselstudien uber unspezifische Therapie *Ztschr f klin Med* **106** 717 1927

urinary work, such focal reactions have been deliberately invoked as provocative tests of distinct diagnostic and therapeutic merit⁵⁹

Under stimulation of inflammatory foci of noninfectious origin have been grouped ocular and renal lesions, such as nephritic retinitis and pain at the site of recent fracture

Under stimulation of latent diathetic phenomena have been grouped attacks of asthma, epilepsy, gout, tabetic crises and delirium tremens among patients who are victims of chronic alcoholism

Mechanism of Focal Reactions—Further experience with and study of unusual reactions will be necessary to determine the correctness of the clinical classification just given. It seems difficult to place in this clinical grouping such reactions as acute vascular thrombosis, anuria and glaucoma occurring in apparently normal eyes. The production of massive thrombi probably requires preexisting vascular disease. Brown also has concluded that it probably requires arteriosclerotic vascular disease, as it has never occurred in uncomplicated cases of thrombo-angitis obliterans in which protein therapy was used. However, Hektoen and Irons⁶⁰ reported a severe reaction and pulmonary embolism occurring immediately after a subcutaneous injection of polyvalent stock vaccine for thrombophlebitis.

Allergy or anaphylaxis as the cause of focal reactions has been suggested, among others, by Kolmer⁶¹ and by Gottschalk⁶². Apart from the massive thrombi seen in these cases of vascular disease, it must be remembered that small thrombi are part of the pathologic manifestations of anaphylactic and anaphylactoid events. It has been suggested that all of these untoward reactions have as their common pathologic basis small thrombi which, in turn, are due to a common immunologic alteration, such as allergy or anaphylaxis. Sollmann, however, has expressed the belief that foreign protein therapy does not elicit an immune reaction but a pharmacologic reaction.

Details concerning the sudden "anaphylactic" deaths reported are, in general, meager. Although some have expressed the belief that

59 Holloway, J. K., and Von Lackum, W. H. Chronic Prostatitis with Special Reference to Its Focal Aspects, *M. J. & Rec.* **122** 64 (July 15) 1925.
Muller, Rudolf. Die Behandlung des venerischen Bubo mit Milchinjektion, *Wien klin. Wchnschr.* **32** 780 (July 10) 1919.
Neverman, Hans. Eine intrakutane Provokations-Methode bei der weiblichen Gonorrhoe, *München med. Wchnschr.* **1** 141 (Feb. 4) 1931.

60 Hektoen, Ludvig, and Irons, E. E. Vaccine Therapy, *J. A. M. A.* **92** 864 (March 16) 1929.

61 Kolmer, J. A. A Practical Text-Book of Infections, Immunity and Biologic Therapy with Special Reference to Immunologic Technic, ed. 3, Philadelphia, W. B. Saunders Company, 1924.

62 Gottschalk, Alfred. Umstimmung des Zellstoffwechsels als Grundlage pathologischer Reaktionen, *Klin. Wchnschr.* **1** 109 (Jan. 15) 1923.

anaphylaxis does occur after protein therapy (Nakazawa,⁶³ Valléry-Radot,⁶⁴ Teague and McWilliams,⁶⁵ van Randenborgh,⁶⁶ Kross⁶⁷), others have expressed their belief that true anaphylaxis does not occur, in that eosinophilia or bronchial spasm are not evident (Miller and Lusk,³ Cowie and Calhoun,²⁶ Greenthal and Brown⁶⁸)

Careful review of the past medical experiences of patients seen in the clinic did not reveal a detectable, significant, common denominator. There was no history of hypersensitivity to protein, known allergy or urticaria. Only two patients had had typhoid fever and these not within recent years.

A brief study of the mechanism of production of the focal reactions, as summarized by Petersen, may help to explain some of the accidents of protein therapy. The injection initiates a sharp clinical departure from the physiologic equilibrium. The most important feature of the reaction is its dual nature, expressed in two phases. The symptoms of the first (negative) phase are increased inflammation, pain, irritability, redness and swelling at the sites of active or latent inflammation. Four main factors are believed to produce these symptoms: (1) An increase in capillary permeability and increased exudation of tissue fluids occur, redness and swelling result, (2) increased tissue pressure is produced, and there is lowering of the threshold for nervous stimuli, increased pain and tenderness occur, (3) there follow increased digestion of inflammatory tissue at foci of circumscribed infection and inflammation, localization of focal reactions is aided by the fact that cells previously involved in an inflammatory reaction respond more readily to all stimuli, and (4) if the resultant necrosis of tissue is great,

63 Nakazawa, F. Influence of Parenterally Administered Protein Substance upon Respiration of Tissue Cell, *Tohoku J. Exper. Med.* **5** 546 (March) 1925.

64 Valléry-Radot, Pasteur. Diagnostic des affections anaphylactiques par les cuti-reactions, méthodes de traitement des affections anaphylactiques, en particulier par la peptonothérapie, *Rev. med. franç.* **8** 39 (Jan.) 1927.

65 Teague, Oscar, and McWilliams, Helen I. The Bacteriolytic Power of Normal and Immune Rabbit Serum for Typhoid Bacilli and the Influence of the Intravenous Injection of Vaccine upon the Same, *J. Immunol.* **2** 167 (Feb.) 1917, Experiments with a Possible Bearing upon Treatment of Typhoid Fever with Typhoid Vaccine Administered Intravenously, *ibid.* **2** 185 (Feb.) 1917, The Bacteriolytic Power of Normal Human Sera and Typhoid Patients' Sera for Typhoid Bacilli and an Inquiry into the Theoretical Basis for the Treatment of Typhoid Fever with Vaccine Administered Intravenously, *ibid.* **2** 193 (Feb.) 1917.

66 van Randenborgh, A. Anaphylaktische Erscheinungen bei Proteinkörper-Therapie, *Zentralbl. f. Gynäk.* **44** 1128 (Sept. 25) 1920, Anaphylactic Manifestations in Proteotherapy, *Zentralbl. f. Gynäk.* **44** 1128, 1920, abstr., *J. A. M. A.* **76** 418 (Feb. 5) 1921.

67 Kross, Isidor. An Experimental Study on the Effects of Protein Injections upon Infections, *J. M. Research* **43**:29 (Jan.) 1922.

68 Greenthal, R. M., and Brown, G. M. Studies on the Nature of Non-specific Protein in Disease Processes, *Arch. Int. Med.* **30** 99 (July) 1922.

there is marked systemic autointoxication from absorption of digested material

The departure from the physiologic equilibrium somehow stimulates a reverse phenomenon which not only restores but overcorrects the inflammatory status, and partial or complete healing is obtained. The various theories regarding the exact mechanism of this stimulation cannot be given. It was Weigert⁶⁹ who first stated that local necrosis at some part of a living organism will, as a rule, result in heightened functional activity. But Arndt⁷⁰ provided the corollary that although weak stimuli accelerate vital activities, strong stimuli inhibit them, and maximal stimuli suppress or utterly destroy them. Hence, if the lytic phenomena of the first phase are excessive, necrosis may get beyond control, without the healing phenomenon of the second phase to compensate for it. In one case the negative phase may be scarcely obvious and the positive phase may rule the picture. Indeed, Cowie has expressed the belief that, in arthritis at least, as far as a reduction of antibody content is concerned, a negative phase is not induced. In another case the opposite may occur, and a positive phase does not seem to follow the negative phase.⁷¹ Then a chronic progression of the inflammatory state may be the deleterious result of protein therapy. Then ulceration, even perforation of certain structures, such as the appendix or cornea, may occur. Thus, as Maliwa¹⁰ has expressed it, the art of protein therapy is not to exceed the desirable limits of this inflammatory process. According to Garrison,⁹ "The crux of the matter is the specific reaction of the individual patient to the threshold dose."

I am still not certain whether these explanations are fully adequate to account for the production of all unusual reactions. Although a change in capillary permeability is among the features noted as part of the normal reaction, such a change is probably usually relatively slight. This change would have to be unusually profound to produce vascular thrombosis, glaucoma and anuria in the presence of normal vascular, ocular and renal function. One must either assume that function or histologic structure was not entirely normal, or that these unusual alterations of function were induced by unusual alterations in permeability. Perhaps, then, a fourth clinical grouping should be recognized, namely, reactions dependent on some marked vasomotor or intravascular chemical change, or on profound disturbances in capillary permeability or colloidal dispersion. This group would include chiefly the vascular accidents, and certainly would provide the most acute, and most of the fatal, reactions.

69 Weigert, quoted by Garrison (footnote 9)

70 Arndt, quoted by Garrison (footnote 9)

71 Laufer, Otto. Ueber die Möglichkeit von Schädigungen durch Protein-Körperinjektionen, *Med. Klin.* **2** 1366 (Sept. 3) 1926

Studies of blood chemistry indicate that no definite burden is put on the kidneys by the reaction, even though many minor variations in renal function are produced. It was reported by Fremont-Smith⁷² that in the first phase a degree of antidiuresis is produced that may at times approach anuria. In the second phase antidiuresis may continue, or diuresis may begin and may continue the subsequent day. My studies on the excretion of phenolsulphonphthalein at different stages in the reaction disclosed that the excretion of dye may be reduced as much as 50 per cent during the second phase, with a subsequent prompt return to normal. These alterations in renal function may have a vascular basis.

Petersen and Miller expressed the belief that vasodilatation of renal vessels occurs in the first phase, vasoconstriction, in the second. Mendelsen's⁷³ expressed opinion was that the renal vessels are constricted, but at what stage, he did not mention. The general vascular changes include reduction of peripheral blood pressure in the first and second phases, at times, considerable reduction in the latter phase. Capillary permeability is thought to be increased in the first phase and decreased in the second phase. The condition of the cutaneous capillaries is not definite. Fremont-Smith and his co-workers reported marked stasis of capillary blood in the first stage and rapid flow in the second. Brown⁷⁴ has noted variability, depending on whether the patient had normally warm or normally cold hands. In general, there was a slow flow, or stasis, in the prodromal (latent and chill) phase, with increased flow in the subsequent phases. It was the slowing of the peripheral flow of blood in the first stage to which Allen and Smithwick attributed thrombus formation.

Although the fatal anuria in one of my cases was in association with iliac thrombi, and in another with a diffuse renal lesion, in the third case there was neither nephritis nor thrombus. Antidiuresis is concurrent with fever, but in this case there was no prolonged fever. It is but speculation to suggest that the anuria was the result of a disturbance of renal vascular (vasomotor) physiologic processes which was not followed by reestablishment of the normal condition. If it is true that the vasomotor status in the viscera is opposite to that in the periphery in the first stage, and that both undergo, in the second stage, complete reversal to the opposite status, one might suggest either that an extensive vasomotor or intravascular chemical change, resulting in thrombosis, or that a vasomotor imbalance set in a state of irretrievable

72 Fremont-Smith, Frank, Morrison, L. R., and Makepeace, A. W. Capillary Blood Flow in Man During Fever, *J. Clin. Investigation* 7: 489 (Aug.) 1929.

73 Mendelsen, Walter. On the Renal Circulation During Fever, *Am. J. M. Sc.* 86: 380 (Oct.) 1883.

74 Brown, G. E. Personal communication to the author.

decompensation is induced. These possibilities are particularly tenable in cases of vascular disease, for instance, of arteriosclerosis.

Relation of Dose of Vaccine to Reactions—Dosage seems to be of variable significance in the production of undesirable reactions. Untoward reactions have occurred after very small doses administered intramuscularly as well as intravenously. In my series the reactions all followed small doses. Contrarily, many physicians have used purposely, and others by mistake, very high doses with impunity. Cowie and Calhoun, Howard and others repeatedly used intravenously, without accident, doses as high as from 1,500,000,000 to 2,500,000,000 typhoid organisms. Although the dose in the fatal case reported by Iions⁷⁵ was high (5,000,000,000 organisms), he and Jobling⁷⁶ have stated that similarly high doses of various organisms have been given without apparent harm. The size of the dose only, therefore, cannot be blamed for unusual reactions.⁷⁶

Regarding high doses, let me note here an unusual reaction that occurred elsewhere subsequent to an injection of 2,000,000,000 typhoid and paratyphoid bacilli by mistake. A patient with thrombo-angitis obliterans was seen at the clinic in 1928. After fair relief had followed an initial injection of 125,000,000 bacilli, he was advised to have similar treatment continued at home. Through a misunderstanding on the patient's part, the physician at the patient's home was induced to give two injections, each of which contained enormous doses. The second dose was later estimated to have been of at least 2,000,000,000 organisms. The reaction was intense. A temperature of from 104 to 106 F lasted for three weeks. Gangrene of the right foot promptly occurred, and amputation was necessitated a few weeks later.

Although large doses may be tolerated, small doses if accompanied by an adequate reaction, seem preferable, since as beneficial results seem to follow the use of the small doses as the large doses. Regarding frequency of doses, Howard⁴⁹ reported giving, without harm, fifty-seven injections intravenously to a patient over a period of eleven months.

Contraindications—There are certain contraindications to treatment by foreign protein. These are as follows: (1) marked arteriosclerosis, peripheral or renal, (2) uncompensated cardiac (Cowie), renal (Miller) or vasomotor (Cecil) disease, (3) chronic infections of long duration, with dissemination to several sites, (4) states of exhaustion following prolonged illness (Miller), (5) pulmonary tuberculosis, active or quiescent, (6) conditions in which hemorrhage may occur, such as

⁷⁵ Jobling, J. W. The Influence of Nonspecific Substances on Injections, *Arch Int Med* **19** 1042 (June) 1917.

⁷⁶ The American and French billion equals one thousand million, and the English and German billion equals a million million.

hemophilia, in patients subject to frequent bleeding, such as epistaxis, and in the ulcerating stage (third week) of typhoid fever (Snyder,⁷⁷ Jobling), (7) the period within fourteen days after an operation, for hemorrhage has occurred occasionally when vaccine was given within ten days after tonsillectomy or minor pelvic operations, (8) marked hypertension (Miller), (9) chronic alcoholism, for fear of delirium tremens (Scully, Muller), (10) states of grave nervous instability (Scully), quiescent or active, such as hyperthyroidism (Miller), epilepsy and certain psychopathic conditions other than dementia paralytica, (11) definite protein hypersensitivity, suggested by a history of serum-sickness, urticaria or angioneurotic edema (Betz⁷⁸), (12) pregnancy, for fear of inducing hemorrhage and uterine muscular contractions (Snyder, Betz, Ichikawa), (13) rheumatic fever with acute or decompensated carditis (compensated cardiac disease has not been considered a contraindication [Miller]), and (14) diabetic acidosis (Woods⁷⁹), the treatment has been safely used at the clinic in controlled diabetes coexistent with arthritis

Certain investigators do not consider endocarditis a contraindication Miller has tried protein therapy in cases of septic endocarditis, and Gross⁸⁰ and Cecil have employed it safely in cases of rheumatic fever with endocarditis Others feel that it can be used with safety, if with caution, in hypertension, pregnancy (Campbell), disseminated infection, typhoid fever (Fairley, Miller), hypersensitivity, menstruation (Campbell) and severe anemia (Miller) Infancy and age (Laurie) have not been considered contraindications, provided that with age the vascular system particularly seems materially sound

Regarding the safety of protein therapy in pulmonary tuberculosis there are different opinions Schmidt and Kraus⁸¹ and Campbell reported pulmonary focal reactions in tuberculous patients, and Matthes⁸² in tuberculous animals, after injections of protein In the review of Hektoen and Irons are cited five deaths from activation of latent pulmonary tuberculosis by the use of stock mixed vaccines On

77 Snyder, R G A Clinical Report of Nonspecific Protein Therapy in the Treatment of Arthritis, *Arch Int Med* **22** 224 (Aug) 1918

78 Betz, Isidor Treatment of Arthritis by Nonspecific Therapy, *M Rec* **99** 920 (May 28) 1921

79 Woods, A C Protein Therapy, Specific and Nonspecific in Ophthalmology, *Ohio State M J* **23** 740 (Sept) 1927

80 Gross, J G Foreign Protein Injections in the Treatment of Acute Infections, *Journal-Lancet* **37** 764 (Nov 15) 1917

81 Schmidt, R, and Kraus, Otto Ueber Proteinkorpertherapie bei Tuberkulose, *Med Klin* **1** 503 1919

82 Matthes, quoted by Petersen, W F Factors in Resistance to Tuberculosis, *Arch Int Med* **21** 14 (Jan) 1918

the other hand, in experiments on animals Baldwin and L'Esperance⁸³ believed increased fibrosis and resistance were provided, whereas Brown, Heise, Petroff and Wilson⁸⁴ noted focal activation in only 2 of 124 tuberculous patients given antityphoid immunization. Similar safety was reported by Clovis and Mills.

Unusual reactions have been noted much more frequently on the arthritic and vascular services than elsewhere at this clinic. In the section on dermatology and syphilology much larger doses are given than on the arthritic service, yet untoward reactions are rare. In certain intractable cases of neurosyphilis, progressive doses reach the amount of several billion organisms given intravenously. In a very few cases, petechiae, jaundice or reactivation of malaria have been noted⁸⁵. This would seem to emphasize what was stated previously, that the reaction does not depend only on the material or dose used, but on the type and extent of the patient's illness. In severe chronic infectious arthritis it is recognized that the pleura, pericardium, spleen and lymph nodes often endure the disseminated infection or inflammation. Such dissemination may explain the preponderance of reactions in this group of patients. In these cases, especially when there is a history of recent pleurisy, pericarditis, myocarditis or abdominal infection, special care may be necessary. There must be some regenerative power left in affected tissues to obtain good results. Although exhaustion and disseminated inflammation may mitigate against the best results, one may not always be justified in withholding the possible benefits of such treatment in those cases in which relief is most desired and difficult to obtain, and when previous treatment has failed (Cecil).

Prevention of Untoward Reactions—Prevention of untoward reactions may be possible. It is dependent on (1) familiarity with the substance used, (2) moderate dosage, (3) careful selection of patients, (4) care of the patient during the reaction, and (5) continuation of the treatment only if the reactions are well borne and satisfactory relief is obtained.

Most important is the selection of patients with due regard to the contraindications noted. Inquiry into the history may suggest the possibility of the presence of quiescent infection from past illnesses. In the presence of marked exhaustion, disseminated infection with little evidence of resistance on the patient's part, or marked arteriosclerosis,

⁸³ Baldwin, H., and L'Esperance, E. S. The Influence of Typhoid Vaccine on Tuberculous Guinea-Pigs, *J. Immunol.* **2** 283 (April) 1917.

⁸⁴ Brown, Lawrason, Heise, F. H., Petroff, S. A., and Wilson, G. E. A Study of the Effects of Typhoid Fever and Antityphoid Immunization on Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **2** 717 (Feb.) 1919.

⁸⁵ O'Leary, P. A., and Goeckerman, W. H. Personal communication to the author.

protein therapy by a more conservative method than the intravenous injection of vaccine should be the method of choice. The vascular and vasomotor alterations induced by a marked reaction may be poorly borne. The proteins that entail milder reactions and the more conservative (intramuscular) method of administration may be permitted.

Although hospitalization during treatment is advisable for patients who are seriously ill, or if it is suspected that an untoward reaction or focal stimulation might occur at the clinic, treatment is administered to large numbers of selected persons who remain as outpatients. Patients should be advised what constitutes the symptoms of a normal reaction, so that unusual phenomena may not be ignored.

To avoid gastro-intestinal symptoms if possible, it is better that no food should be taken from two to four hours prior to an injection. However, many tolerate injections without such restriction of food.

The patient should go to bed within a half hour after the injection, and remain there during the reaction. To lessen the discomforts of the reaction especially the period of chill, hot water bottles and mild analgesics should be supplied. It has been noted that the local application of heat prevents stasis of the blood in peripheral capillaries, which occurs in the first stage, or it abolishes stasis once it has occurred. Fluids should be given during the treatment, especially if reactions are associated with definite loss of weight.

The reaction can be shortened and discomfort lessened, according to Scully²⁴ Myers⁴² and Perkins and White⁸⁶ by preceding the injection with a small dose of codeine or morphine given hypodermically, and by giving from 5 to 10 minims (0.31 to 0.61 Gm.) of epinephrine chloride (1:1000 solution) subcutaneously after the chill. Heat may suffice instead of epinephrine. It may be argued, however, that minimizing the reactions thus may lessen the chances for ultimate benefit. Duke⁸⁷ has expressed the belief that unusual reactions may be prevented by mixing very small doses of epinephrine and ephedrine with the vaccine.

Early Recognition—In eight of my fourteen cases in which unusual reactions occurred, the reaction appeared after the initial dose. In the experience of Zimmer and Buschmann,⁸⁸ focal reactions usually occur after the first injection and, if they recur, may be of minimal severity, and finally may cease to occur. The approach of unusual reactions frequently can be recognized by attention to unusual complaints on the part of the patient. Pain in the thorax or precordium may signalize

⁸⁶ Perkins, R. J., and White, G. B. Rheumatoid Arthritis Treated with Intravenous Bacillus Coli Vaccine, *Brit. M. J.* **1**: 411 (March 10) 1923.

⁸⁷ Duke, W. Personal communication to L. G. Rowntree.

⁸⁸ Zimmer, Arnold, and Buschmann. *Paul. Aus der chirurgischen Universitäts Klinik, Ztschr. f. ärztl. Fortbild.* **22**: 513, 1925.

pleurisy or pericarditis. Unusual degrees of nausea and anorexia or the appearance of diarrhea or of localized abdominal tenderness may mark the onset of enteritis or focal activation in the appendix, gallbladder or pelvis. A sharp, continued pain in the region of a large blood vessel during the period of chill, or at the end of it, may denote the formation of thrombi. If the patient's fever continues longer than from eighteen to twenty-four hours after the injections, reexamination of the thorax and abdomen is indicated. The leukocytosis (from 15,000 to 40,000 leukocytes per cubic millimeter of blood) induced by the reaction usually disappears after from twenty-four to forty-eight hours. If it remains high, an explanation should be sought. An adequate output of urine the day of the injection and for two days subsequent to it, should be inquired for and insured.

Treatment of the Reaction—The treatment in cases of unusual reaction does not differ in general from the treatment of such phenomena when they are not induced by protein therapy. When frank instability of vascular physiologic processes occurs, it should be treated on the basis of the knowledge of the vasomotor alterations induced, particularly in the first or negative phase of the reaction. If vascular accidents occur, such as thrombi or vasomotor depression, the patient should be kept in bed, and warm applications should be used. If possible, thrombi in peripheral vessels should, of course, receive prompt surgical care. Gow,⁸⁹ stressing the possible anaphylactic nature of some of the reactions, relieved dyspnea and cyanosis by injections of epinephrine (0.75 cc. of a 1:1,000 solution) or one-hundredth grain (0.6 mg.) of atropine sulphate. In this connection the experimental work of Hanzlik and Karsner⁹⁰ on the prevention or amelioration of anaphylactoid phenomena from intravenous therapy by the use of atropine and epinephrine is of interest. If renal insufficiency and oliguria occur, the intravenous administration of diuretics is indicated.

The activation of latent inflammatory foci, if kept within control, should not be looked on as an untoward reaction. Indeed, it should be regarded as a fortunate demonstration of unsuspected infection. Thus the procedure constitutes a legitimate provocative test. Theoretically, the possible harmful phenomena of the first phase are safely reversed by the second phase. It may not always be safe to rely on this, however. For example, if acute appendicitis is discovered, the usual surgical indications prevail.

⁸⁹ Gow, A. E. Intravenous Protein Therapy, *Brit. M. J.* **1**:284 (Feb. 28) 1920.

⁹⁰ Hanzlik, P. J., and Karsner, H. T. Anaphylactoid Phenomena from the Intravenous Administration of Various Colloids, Arsenicals and Other Agents. A Comparison of the Prophylactic Effects of Atropine and Epinephrine in Anaphylactic Shock and Anaphylactoid Phenomena from Various Colloids and Arsphenamine, *J. Pharmacol. & Exper. Therap.* **14** 379 and 425 (Jan.) 1920.

SUMMARY AND CONCLUSIONS

The reactions to injections of foreign protein (typhoid vaccine intravenously) have been studied in a group of about 2,500 patients, representing an aggregate of about 10,000 injections. Of these 2,500 patients approximately 1,500 were on the arthritic service and 1,000 on the vascular and other services.

The reactions have, in general, been well borne, and the beneficial results from protein therapy justify, in certain diseases at least, its continued use and further development.

Unusual reactions to such treatment have been rare at the clinic. They have occurred in this series in fourteen cases in all, an incidence of about 0.5 per cent of the patients. They occurred seventeen times in the treatment of twelve patients with arthritis (including one patient with rheumatic fever) and three times in the treatment of two patients with occlusive vascular disease. Thus, of 10,000 injections only twenty were followed by an unusual reaction, an incidence of 0.2 per cent of the injections.

Unusual reactions subsequent to the injections were as follows: acute and subacute appendicitis, cholecystitis, enteritis, pleurisy, pericarditis, iritis, glaucoma, adenitis, extensive vascular thrombosis and renal insufficiency. In arteriosclerotic vascular disease, acute thrombosis is the occasional possibility. In arthritis and other diseases, the reactions are variable. It is believed that these reactions are not incidental complications, but are related to protein therapy in the presence of an underlying disease.

Death occurred in three instances, a mortality rate of 0.12 per cent. This constitutes a very small risk, but a risk that must be recognized and that can possibly be avoided by the most careful selection of patients.

Unsuspected latent or quiescent focal inflammation and infection may be stimulated. Except in certain conditions, of which pulmonary tuberculosis is one, the known presence of latent or quiescent foci should not act as a contraindication to such treatment. Indeed, part of the value of such treatment lies in the possible demonstration of suspected or unsuspected foci otherwise undemonstrable at the time. Such reactions, if their significance is appreciated, may be advantageous rather than detrimental.

The mechanism of the usual and unusual reactions can be understood in part at least, from study of the various reported components of the reactions.

Unusual reactions have been considered previously as being of three types, for they resulted mainly in one of the following: (1) stimulation of inflammatory foci of infectious origin, (2) stimulation of inflammatory foci of noninfectious origin or (3) stimulation of latent diathetic

phenomena There may be a fourth type of unusual reaction, one dependent on some marked vasomotor or intravascular chemical change which may produce acute thrombosis or vasomotor imbalance Advanced sclerosis of peripheral coronary or renal arteries must be stressed as a possible contraindication in addition to those mentioned by others Particularly must this be taken into consideration in the treatment for occlusive arteriosclerotic vascular disease of the extremities

The prevention, recognition and treatment of unusual reactions is considered

The assembly here of the unusual reactions experienced at the clinic and elsewhere, it is hoped, will not give them an undue emphasis, to the detriment of a useful and essentially safe form of treatment The recognition that such reactions may occur has led me to a more careful selection of patients and a more judicious use of protein therapy

THE QUANTITATIVE DETERMINATION OF THE POTENCY OF LIVER EXTRACT *

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In a previous communication ¹ it was demonstrated that liver extract had a marked influence in ameliorating the signs and symptoms of pernicious anemia of the fowl. The present paper deals with the same subject on a quantitative basis.

As already discussed,¹ a disease complex, analogous in all important respects to pernicious anemia in human beings, can be separated from the pernicious anemia-leukemia syndrome of Ellermann ² as it occurs in fowls. Moreover, it can no longer be doubted that, in fowls, the leukanemic or aleukemic leukotic cases, that is, cases with symptoms and signs of pernicious anemia but with myelocytic proliferations in various organs, especially in the liver, belong essentially to the pernicious anemia group and not to the leukotic one. Pernicious anemia, therefore, as it occurs in the fowl, is quite a distinct and separate disease in every respect, especially as regards etiology, from leukemia or leukosis. There are no borderline or transitional cases, such as leukanemias might be considered, bridging the gap between the one state and the other. The present investigation makes use of cases of pernicious anemia so defined as the basis of the experimental work.

The fowls employed were white leghorns of various ages, the subjects of a spontaneous attack of the disease. The condition in the different cases had progressed to varying degrees of severity.

While under observation, they were confined singly in cages, inside a house. They were fed, ad libitum, on a bran and sharp mash and mixed grains, and had free access to water and oyster shell grit. As they were still on the same ration as before but no longer on free range, their conditions were not so liberal as those under which they had contracted the disease.

The various medicinal agents were administered twice daily, at 9.30 a.m. and again at 2 p.m. This daily twofold dosing has to be borne in mind in reading the accompanying charts, which indicate only the points where a certain treatment or change of treatment was com-

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From the Rowett Research Institute

1 McGowan. Edinburgh M. J. **37** 330, 1930

2 Ellermann. The Leucosis of Fowls and Leukaemia Problems, Gyldeudal, 1921

menced As a rule the fowls received any one dose for two days before a change was made to the next higher one

The observations recorded were made for the purpose of arriving at the smallest dose of liver extract which would produce a noticeable and significant effect on the blood curves They deal, thus, with the effect of administration of liver extract in conjunction with iron and ammonium citrate by mouth, of liver extract intraperitoneally with iron and ammonium citrate orally, and finally of liver extract intraperitoneally without iron The description follows the same sequence The amount of iron and ammonium citrate administered was constant throughout the series and consisted of 0.5 Gm given twice daily

The liver extract employed was no. 343, in three batches³ When given by mouth it was dissolved in water and administered by means of a rubber teat pipet, when intraperitoneally, it was suspended in ether—the ether being allowed to evaporate slowly—dissolved in sterile saline solution and injected

In the description of the results obtained in this investigation, much of the important information gleaned has been incorporated in the charts A short explanation, therefore, of each chart with a discussion of points special to each case will be all that is required by way of letterpress As it is not germane to the present issue, no cognizance will be taken, in the description of bone marrow changes, of the finer details, such as the alteration from a hemocytoblastic-amitotic to an erythroblastic-mitotic basis in the formation of the erythrocytes¹ The description will center round what is more important in the present instance, the occurrence of sclerosis of the bones, the disappearance of the marrow tissue, and the question as to whether the marrow, histologically, is in a normal, "hyperplastic"⁴ or aplastic condition

DESCRIPTION OF CASES

HEN 344 (chart 1) —On the third day after the commencement of the administration twice daily of one-fourth phial⁵ of liver extract by mouth, there was a slight rise of both the hemoglobin and red blood cell curves, which persisted for a short time The subsequent administration of one-fourth phial, intraperitoneally, however, produced no effect It demonstrated, however, that the extract could with care be given intraperitoneally, without injurious local effect

The marrow in this case was in a very aplastic condition—indeed, in the tibia it had entirely disappeared, leaving large fatty oily cavities filled with a clear fluid There was considerable sclerosis of the bones In all probability the

3 Supplied by Eli Lilly & Company, Indianapolis

4 Hyperplasia of the pernicious anemia type

5 To avoid the repetition of this cumbersome phrase, future references will merely give the fraction and the phial and leave the rest to be understood The word phial refers to the receptacle in which each dose is separately contained for human use

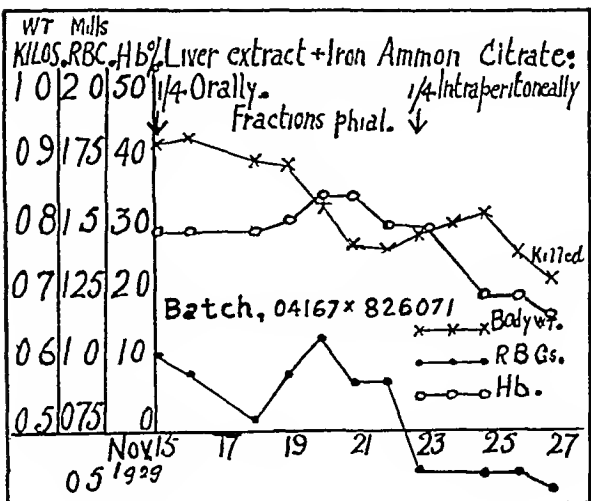


Chart 1—Results in hen 344

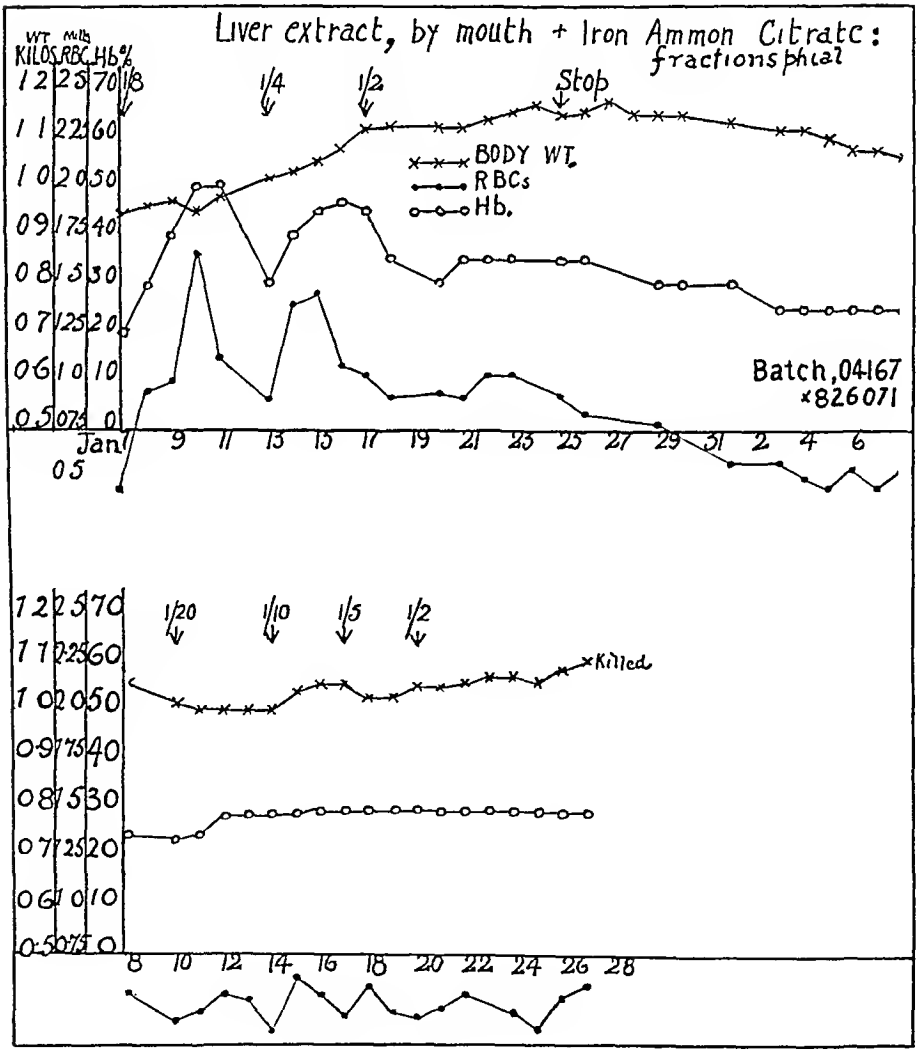


Chart 2—Results in hen 350

degeneration of the marrow was responsible for the small and fleeting reaction obtained and for the ineffectiveness of the subsequent intraperitoneal injections

HEN 350 (chart 2)—This fowl showed an almost immediate and very considerable reaction to the administration of one-eighth phial orally. Though this dose was continued, there was a marked fall in the curves in a few days. This was followed by a rise on increasing the dose to one-fourth phial. In its turn this was followed by a fall which persisted in spite of the dose being raised to one-half phial. On January 25, the liver extract and the iron were stopped and the hemoglobin and red blood cell curves continued to fall. On February 10, treatment was recommenced, this time with very small doses of the liver extract. The most that can be said with regard to its effect on this occasion is that there was a slight rise in the hemoglobin curve while the red blood cell curve became more unstable and irregular.

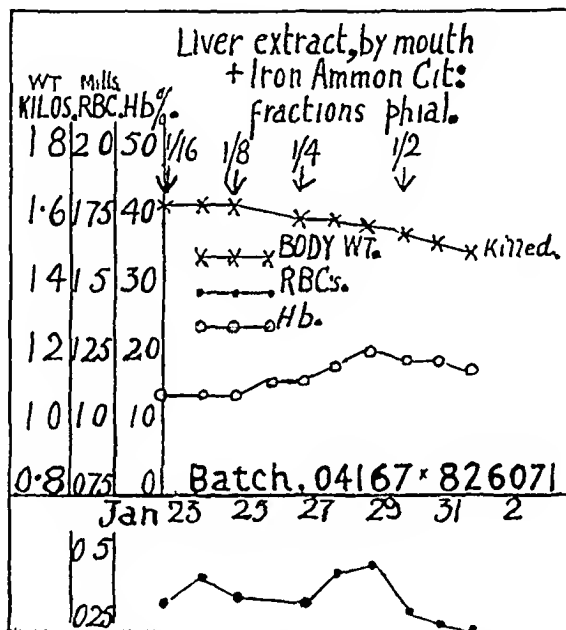


Chart 3—Results in hen 353

On being killed on February 26, the fowl was found to be suffering from marked ascites. This in all likelihood was responsible for some of the increased weight observed. There was a fair amount of sclerosis of the bones, with a reduction in the quantity of marrow. The marrow itself was hyperplastic in type.

HEN 353 (chart 3)—In this case there was a very slight and doubtful response in the hemoglobin and red blood cell curves, which began with the administration of one-eighth phial. The bones were considerably sclerosed and the marrow was in the same aplastic and degenerated condition as in hen 344.

HEN 358 (chart 4)—In this case the first definite rise in the red blood cell and hemoglobin curves occurred on the administration of one-fourth phial by mouth. This was followed by a more definite rise when one-half phial was given. Later both curves sank considerably, even though the dose had been raised to 1 phial.

The hen died on March 24. It was greatly emaciated, and considerable ascites was present. There was quite definite sclerosis of the bones with reduction of the quantity of marrow. The marrow itself was in a hyperplastic condition.

HEN 361 (chart 5) —In this case the red blood cell and hemoglobin curve commenced to rise on the administration of one-thirty-second phial. This upward tendency increased and reached its height on March 5 during the administration of one-half phial. Shortly after this, on March 9, the curves began to fall and continued to do so although the dose administered was now 1 phial. The dosing was stopped on March 15, when the fall became accelerated.

The fowl was killed on April 4. There was marked old sclerosis of the bones with a great reduction in the quantity of the marrow. The marrow itself was

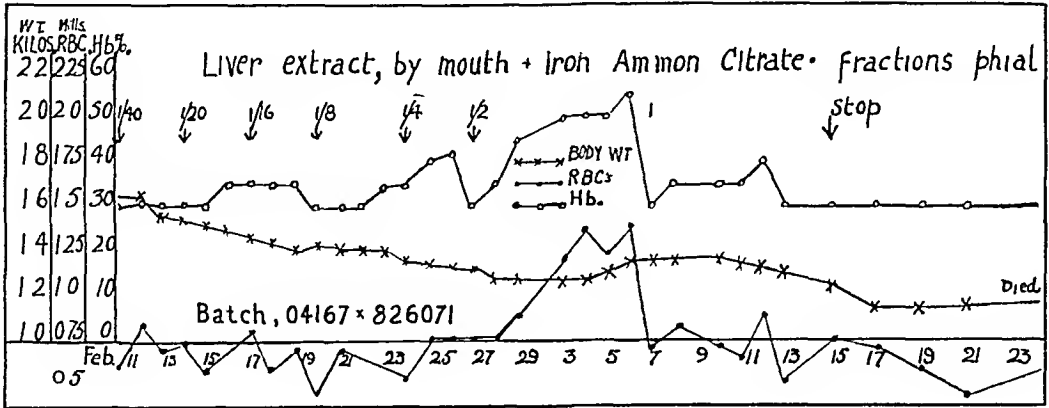


Chart 4—Results in hen 358

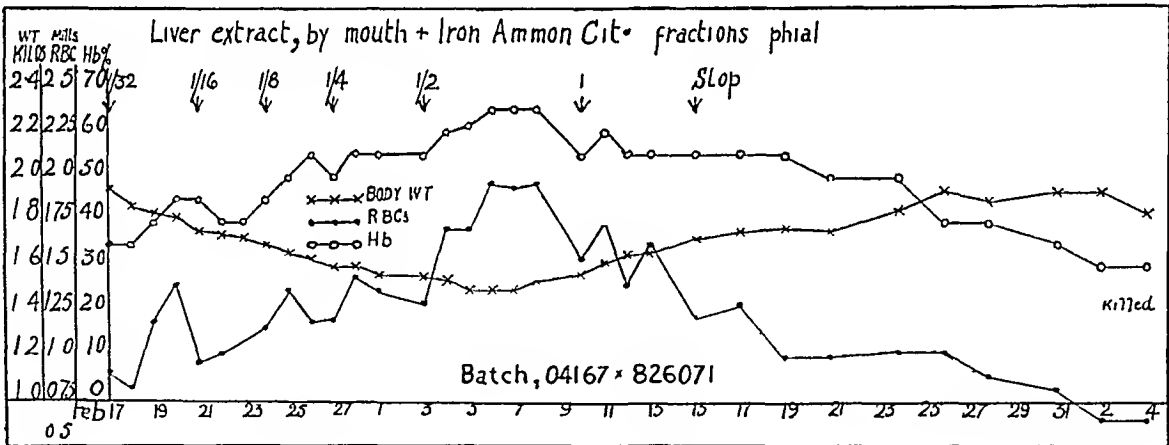


Chart 5—Results in hen 361

of a hyperplastic type. This fowl was fat and muscular and showed no edema or ascites.

HEN 362 (chart 6) —Here there was a small ephemeral rise in both curves subsequent to the administration of one-half phial by mouth. This was followed by a fall which persisted even though the dosage was increased to 1 phial.

The fowl was killed on April 2. It was muscular and fat and without ascites. There was very great sclerosis of the bones with reduction of the quantity of marrow. The marrow itself was in a state of great aplasia, consisting as it did for the most part of fat cells only. This would account for the lack of response in the blood curve.

HEN 363 (chart 7) —Here there was no response, and the hen died in a few days. In this case the bones were so sclerosed that there was practically no marrow left. What was present was in a condition of advanced aplasia.

HEN 369 (chart 8) —In this case, too, there was no response to the administration of liver extract.

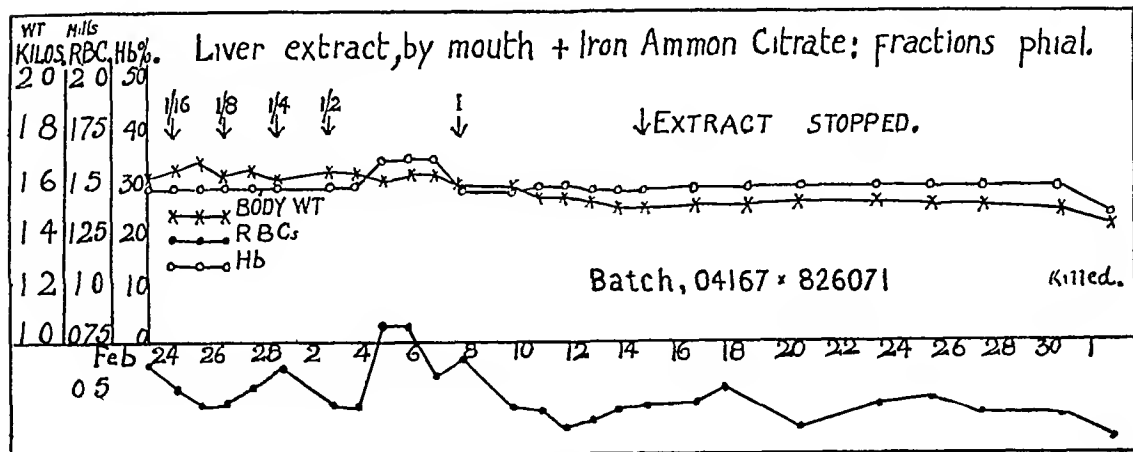


Chart 6—Results in hen 362

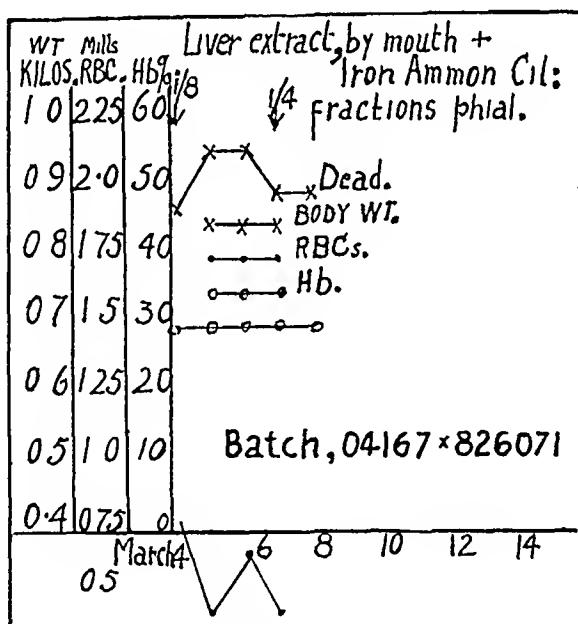


Chart 7—Results in hen 363

The fowl was killed on April 7. The bones were in a condition of advanced sclerosis, and the marrow had practically disappeared. Any that was left was in a condition of advanced aplasia.

HEN 371 (chart 9) —Here the first observation on the blood was made on May 31. An interval elapsed before the next one was made, and the administration of liver extract was commenced on June 22. It is possible that there was a slight response to the administration of one-fourth phial on June 23 and 24. Thereafter there was no reaction in spite of increased dosage and the employment of another batch of the extract.

The fowl was killed on July 8 There was considerable sclerosis of the bones and great reduction of the marrow, which showed marked aplasia

HEN 377 (chart 10)—This fowl was kept under observation for a considerable period and subjected to varied treatments Liver extract, batch 04167 \times 826071, in a dosage of one-half phial, would seem to have produced a slight response, which increased considerably when a whole phial was given A change to batch

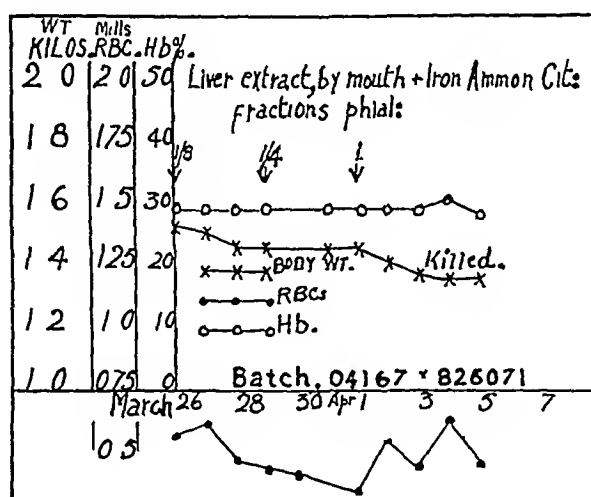


Chart 8—Results in hen 369

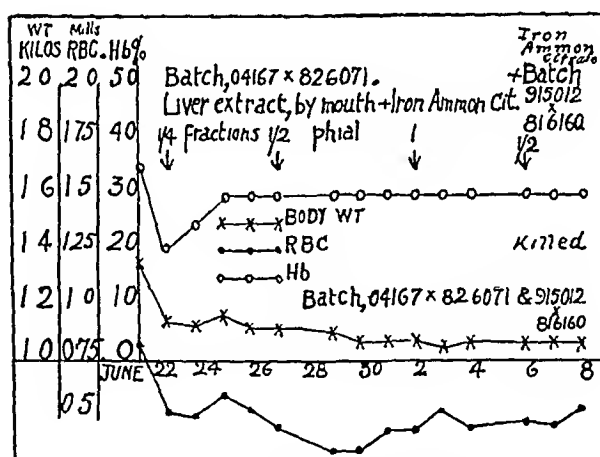


Chart 9—Results in hen 371

915012 \times 816160 maintained the rise, but a fall, which had already commenced, persisted on changing back to batch 04167 \times 826071, even at an increased dosage A change to ox liver now did not improve matters, but a marked though temporary swing up occurred on June 2 on the intraperitoneal injection of one-eighth phial, and again on June 9 on the injection of one-fourth phial All treatment was stopped for a while, but on June 30 and again on July 9 the curves were caused to move up by the intraperitoneal injection of one-fortieth and one-fifth phial, no iron being administered on this occasion The batch employed here was 4 F8 \times 842599

The hen was killed on July 14. There was a considerable accumulation of brown material, possibly inspissated liver extract and necrotic cells, in the peritoneal cavity but no peritonitis. The bones were considerably sclerosed and there was a marked reduction in the quantity of the marrow. This, however, was of a hyperplastic type.

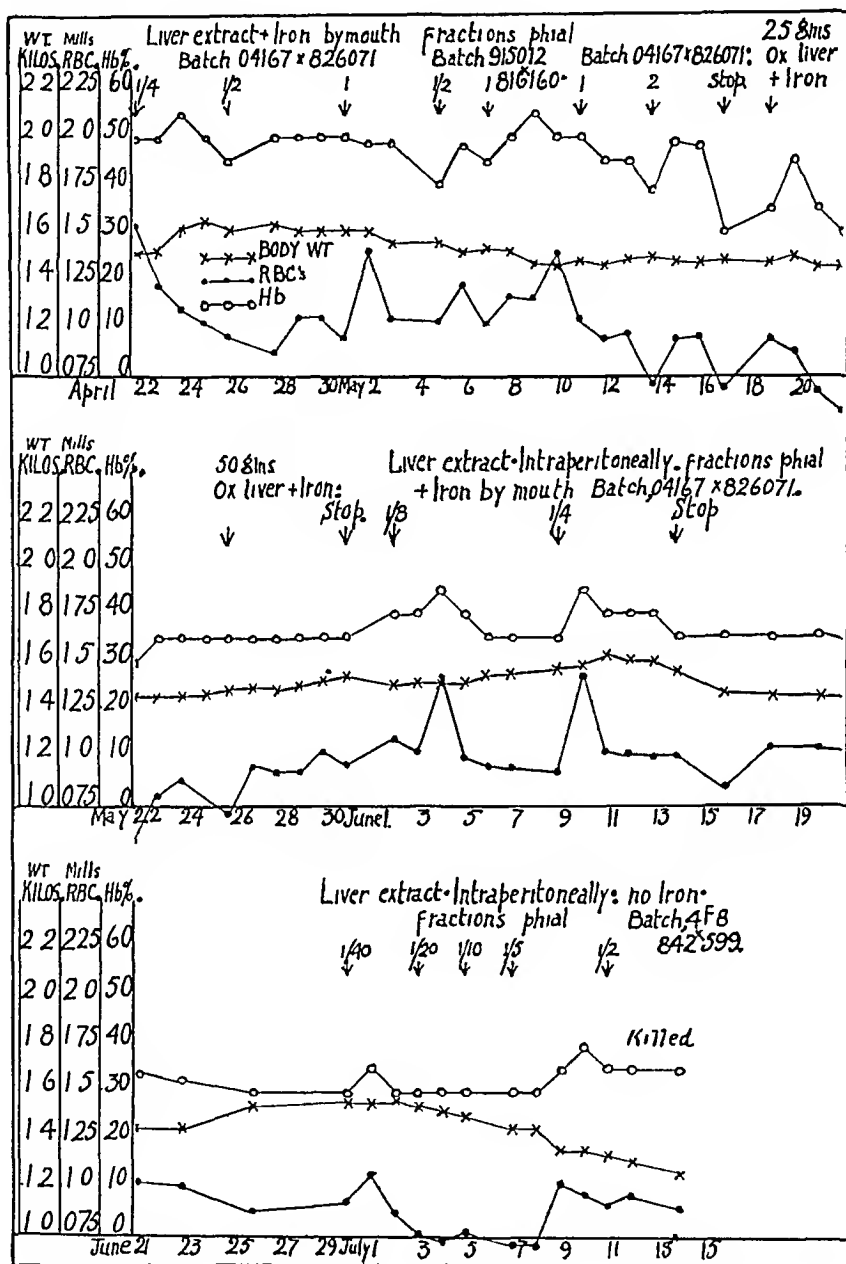
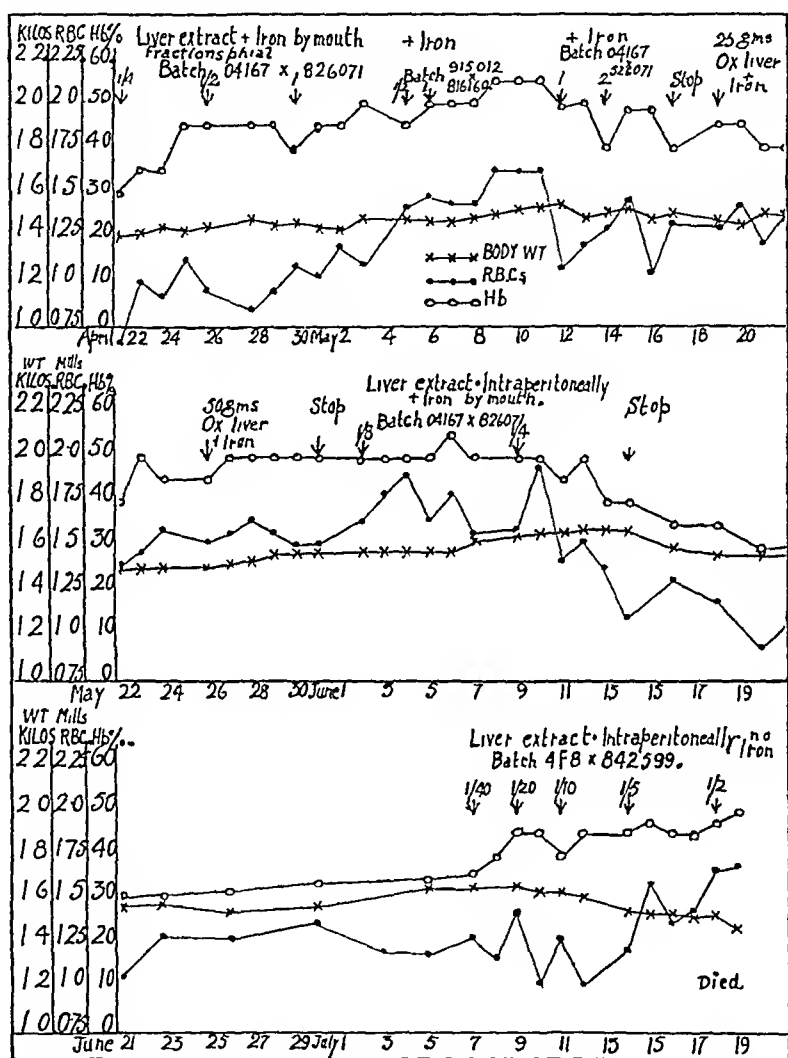


Chart 10—Results in hen 377

HEN 378 (chart 11)—This hen received treatment identical with that of hen 377 during the same period of time. It gave, however, a much better response to treatment with liver extract at every stage of the experiment. Attention need only be drawn to a few special points. On April 21, an immediate response was obtained to the administration of one-fourth phial orally. This rise was sustained through varying dosages up to May 16. The administration of ox liver now, at a time when the curves had fallen somewhat, caused a slight rise. This was considerably increased on the intraperitoneal administration of increasing doses of

liver extract beginning with one-eighth phial. However, on June 13, a fall had set in before this treatment was stopped (June 14). The fall continued till July 7, when a rise in both curves commenced again on the intraperitoneal administration of liver extract in increasing doses beginning with one-fortieth phial. No iron was given on the last occasion, and the batch employed was 4 F8 X 842599.

The hen was found dead on July 19. The peritoneal cavity was greatly distended with brown material as in hen 377. There was considerable sclerosis of the



• Chart 11—Results in hen 378

bones, with reduction of the quantity of marrow. This was of a hyperplastic type.

HEN 379 (chart 12).—This hen was tested with batches 04167 X 826071 and 915012 X 816160 by mouth with the addition of iron. A response was obtained with one-fourth phial of the first batch, this increased somewhat on increasing doses and was not altered by changing to the second batch.

This fowl was killed on May 7. The bones were found to be so sclerosed that there was hardly any marrow left. What remained was in a very aplastic condition.

HEN 384 (chart 13)—Liver was given in the first instance in this case, followed by liver extract This was done in an attempt to gage the potency of the one as compared with the other Little deduction, however, can be drawn

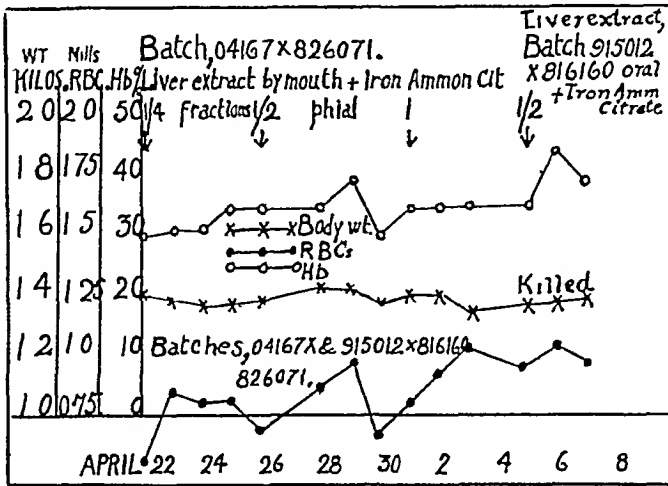


Chart 12—Results in hen 379

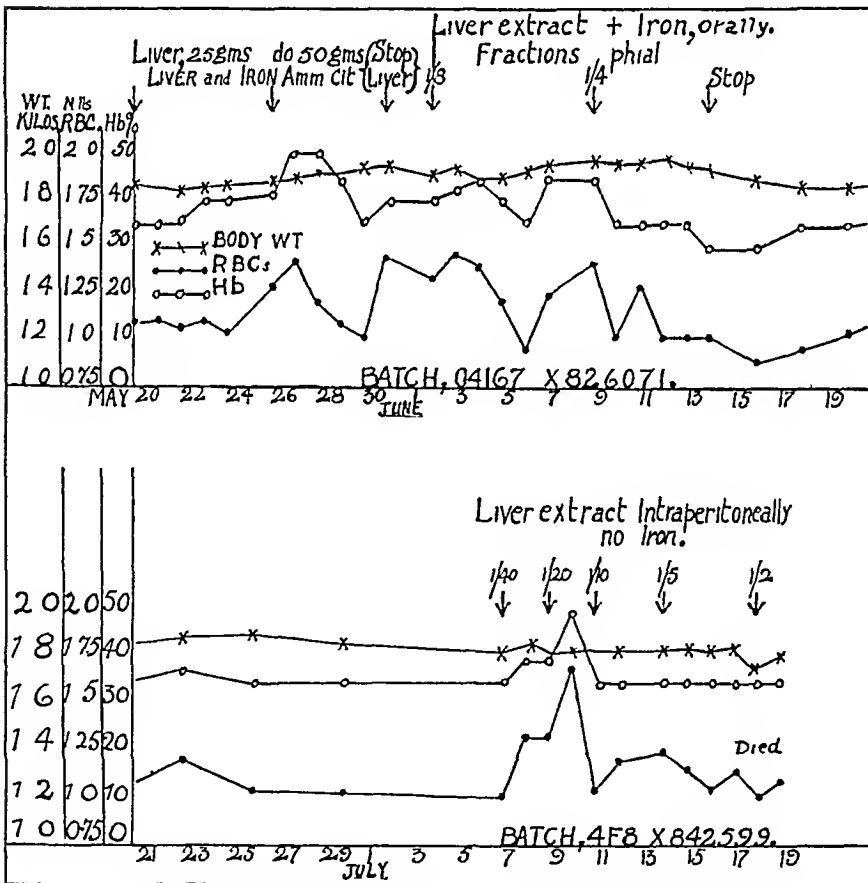


Chart 13—Results in hen 384

from the first part of the curves except that a rise of an irregular type, initiated by the liver, was maintained in a similar irregular fashion by the administration of liver extract This was followed by a fall which persisted after stoppage of treatment on June 14 On July 7, liver extract was injected intraperitoneally with-

out the accompanying administration of iron by mouth, one-fortieth phial at once gave a marked response which persisted for a few days but subsequently fell, even although much larger doses of liver extract were administered

The hen died on July 19 The peritoneal cavity was filled with the same brown material as in hens 377 and 378 The bones were markedly sclerosed and the marrow greatly diminished in quantity The marrow was of a hyperplastic type

Before the next series of observations was commenced, a summing up of the situation had been undertaken It was recognized that, for some reason or other, as judged by the amount of liver extract necessary, the administration of this extract by mouth was much less efficacious in the fowl than in the human being Intraperitoneal injection of a preliminary type had been resorted to with considerably better results Such results, however, had been obtained in cases in which iron had been simultaneously administered by mouth In a previous paper¹ it had been found that iron of itself was of no avail in ameliorating the disease The results obtained in the present series of observations, in which the standard dose of iron was continued for long periods in conjunction with subeffective doses of liver extract without any rise in the curves, add confirmation to this observation In the experiments heretofore the administration of iron had been continued as a routine on the chance that the possible absence of hemoglobin-forming materials might be a limiting factor in betterment of the blood and marrow condition, which the iron would help to rectify

It was now decided to cease the administration of iron and to test the effect on the blood curves of injections intraperitoneally of the liver extract alone It so happened, however, that the two first cases that occurred were of an identical and peculiarly interesting type One of them was therefore employed as a bridging case to the new scheme, and this fowl (hen 387) was in consequence given iron orally

The periods of the lives of fowls 377, 378 and 384 dealt with in the terminal portions of the respective charts (nos 10, 11 and 13) are not included in this section, as these have to deal with the results of intraperitoneal injection of liver extract, without the conjoined administration of iron by mouth It will be noted that in each there is a response in the curves to the dosage of one-fortieth phial

HEN 387 (chart 14) —The administration intraperitoneally of one-fortieth phial of liver extract caused a rapid and extensive rise in the hemoglobin and red blood cell curves, which persisted under daily administration until the fowl was killed, on June 29

The outstanding feature in this case is that the bones showed little or no sclerosis and consequently very slight diminution in the quantity of marrow The marrow itself was hyperplastic in type In addition, and as a characteristic feature, examination of the blood before treatment showed the presence of very large numbers of hemocytoblasts, plasma cell erythroblasts and erythroblasts These observations indicated a very reactive condition of the marrow and almost

certainly are the explanation of the rapid and marked response shown in the chart. As the hemoglobin percentage and the number of red blood cells increased, there was a gradual disappearance of these immature cells until finally the cytology of the blood became practically normal.

HEN 389 (chart 15) —This case is almost identical with the last one, hen 387. There was, however, no administration of iron. As in hen 387, a marked reaction

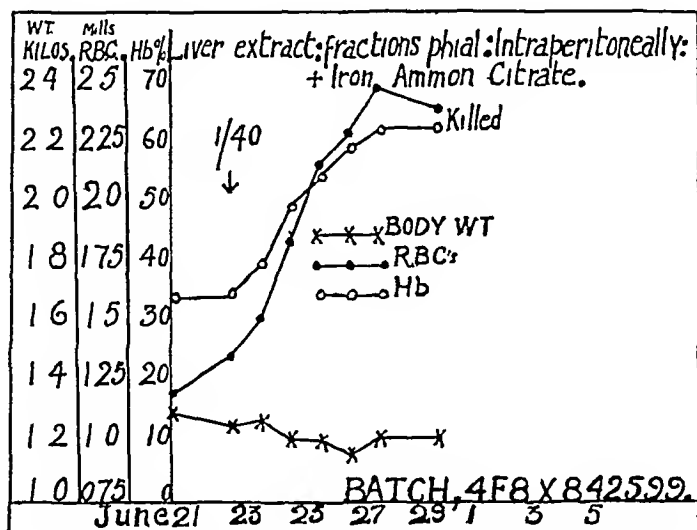


Chart 14—Results in hen 387

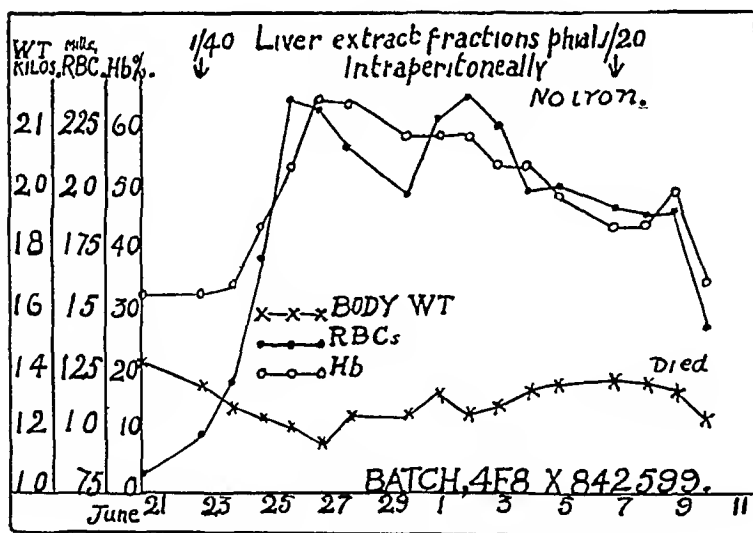


Chart 15—Results in hen 389

in both curves was obtained on the administration of one-fortieth phial of liver extract and on its continuance. After a time, on July 3, the effect began to wane and continued to do so, very little betterment being affected by increasing the dose to one-twentieth phial. The hen died on July 10. The immediate cause of death was a large hemorrhage from the liver. The postmortem observations and condition of the blood were exactly as described for hen 387.

Both cases would appear to be early ones, in contrast to the majority which were under observation. In them the marrow was in a very reactive and responsive condition and had not suffered much reduction

in quantity Hen 317, discussed in a previous communication,¹ behaved similarly on the oral administration of liver extract and observations on its blood before treatment were of exactly the same nature. Such cases would appear to be ideal for the purpose of standardization of liver extract, but unfortunately their occurrence is the exception rather than the rule.

HEN 388 (chart 16)—Owing to the occurrence of holidays and to the fact that this fowl's blood was not considered to be in a sufficiently poor state for testing

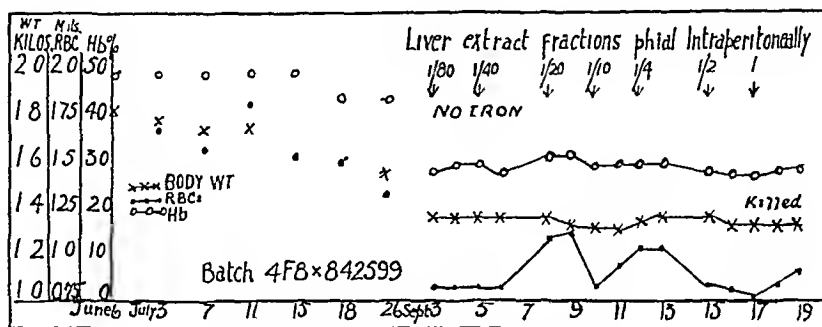


Chart 16—Results in hen 388

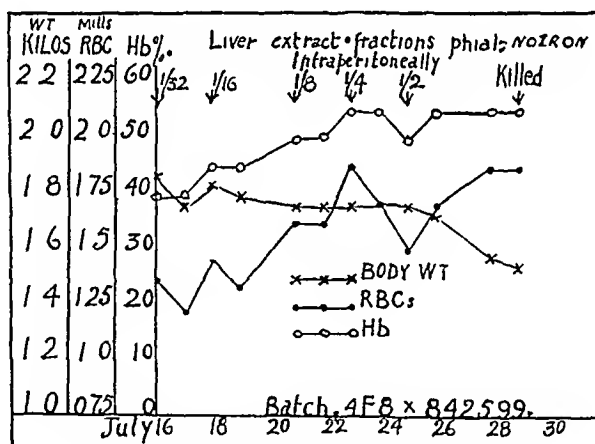


Chart 17—Results in hen 395

purposes, liver extract was not administered during the period covered by the first half of the chart. Observations on the blood were, however, made at intervals. When given, the liver extract was injected intraperitoneally without the accompaniment of iron. There is a definite response shown in the curves to the administration of one-fortieth phial. The reaction, however, is small and fleeting.

On postmortem examination the bones were found to be practically completely sclerosed, and marrow almost nonexistent. Any marrow that was present was in an aplastic state.

HEN 395 (chart 17)—Liver extract was administered intraperitoneally but no iron was given. A response occurred in both curves to a dose of one-thirty-second phial, and the rise continued with increasing dosage.

The hen was killed on July 29 The bones were markedly sclerosed and the marrow diminished in quantity The marrow itself was in a hyperplastic state

HEN 396 (chart 18)—The dosing was as in the previous case A response occurred in both curves to a dose of one-thirty-second phial, and the rise was marked and progressive

The fowl was killed on July 29 There was very little sclerosis of the bones, and the marrow was not much diminished in quality It was in a hyperplastic state

In this case there was exhibited, following the administration of liver, a marked rise in the number of hemacytoblasts, erythroblastic plasma cells and erythroblasts in the circulating blood This condition reached its height about July 23 Thereafter the numbers diminished and the blood became practically normal cytologically At the same time the hemoglobin and red blood cells increased

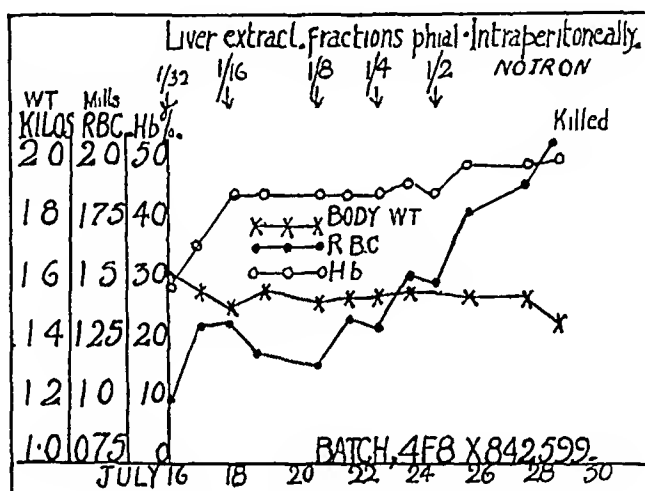


Chart 18—Results in hen 396

This phenomenon occurred to some extent in all the cases on the administration of liver extract It is only, however, in cases with a reactive marrow that it reached proportions of sufficient dimensions to be correctly gaged Owing to this limitation it cannot be used, like the analogous reticulocytosis in cases of human pernicious anemia, as an index for testing the potency of liver extract

HEN 405 (chart 19)—The same dosing was employed as previously A response occurred in both curves to a dose of one-fortieth phial, increasing thereafter with increasing dosage Owing to some factor it was found impossible for a period to count the red blood cells, due to the rapidity with which the blood coagulated The same phenomenon had been observed previously in an occasional fowl with pernicious anemia

The hen was killed on October 27 There was considerable sclerosis of the bones and diminution of the bone marrow The marrow itself was hyperplastic

Although not specifically stated previously, every case dealt with here exhibited the postmortem appearances typical of primary or per-

nicious anemia of the fowl. In addition, several cases—especially among those in which liver extract had been given intraperitoneally for some time—showed considerable myelocytic proliferation in the periportal spaces of the liver. In some instances it reached a degree recalling the condition leukanemia. In quite a proportion of cases, too, the liver was studded all over with minute punctiform hemorrhages. These were found in great part to surround small periportal proliferations of myelocytes. Their significance is not understood. Under the conditions of their origin the administration of liver extract would appear to have something to do with their causation. In cases in which large doses of liver extract had been given intraperitoneally for long periods there was often an accumulation of turbid brown fluid containing inspissated brownish flakes in the peritoneal cavity. The brown

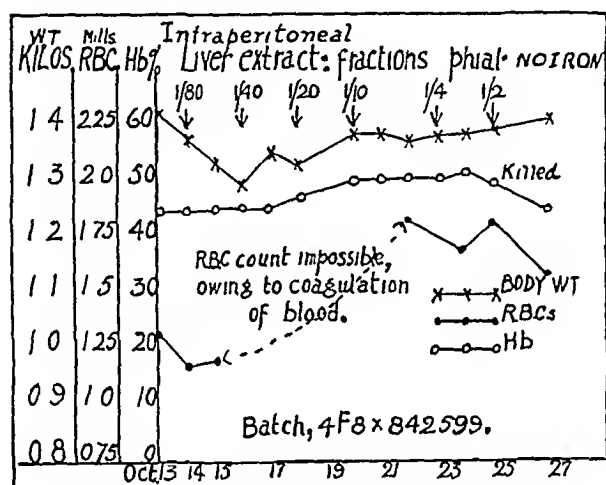


Chart 19—Results in hen 405

substance consisted in great part of necrosed cellular remains. It was striking, however, how rarely anything of the nature of an acute peritonitis occurred. When small doses were given for short periods, the peritoneal cavity was completely normal in appearance.

A survey of the cases described brings to view the fact that in practically none of the cases (cases 387, 389 and 396 are possible exceptions) did the hemoglobin percentage and number of red blood cells rise to normal on the administration of liver extract. It will be observed further that, after a preliminary rise to a maximum, there was in every case a subsequent marked fall, even although liver extract in increasing quantities continued to be given. Again, as it happened, many of the fowls died, and without doubt all would have done so in the long run, for a case of permanent recovery in this condition has never been observed.

In a previous paper,¹ reasons were suggested in the individual cases for the deaths of the experimental fowls even after they had been considerably benefited by the liver extract. It is now recognized that, while the reasons adduced on such occasions may have been of a contributory nature, without doubt the essential cause lies in the inherent perniciousness of the condition.

Pernicious anemia in fowls would seem to be, in every respect, a much more malignant and intractable condition than the corresponding disease in human beings. Its occurrence in fowls is also much greater, being in the neighborhood of 3 per cent per annum as compared with 0.005 per cent⁶ in human beings.

The case histories given make it evident that the less bone sclerosis and the larger the amount of hyperplastic marrow present, the greater and more sustained is the improvement in the circulating blood. Furthermore, the cases so far observed show that the circulating blood gives evidence of a response on the part of the marrow to liver extract of a remarkably constant nature. Thus, the rise of the curves for the same extract in different fowls commenced with the same dosage, irrespective of the condition and amount of the marrow, provided only that it was in a hyperplastic state and not aplastic.

The changes occurring in the cytology of the circulating blood in relation to the amount and condition of the marrow have already been described. The resemblance of these phenomena to the reticulocytosis following the exhibition of liver extract in cases of human pernicious anemia has also been alluded to, and the difficulty of using them as an index for purposes of standardization has been referred to. Such observations and conclusions, arrived at some time ago, are supported by the recently published views of Riddle⁷ on the relationship of liver feeding to reticulocytosis. He concluded, much as has been done in the present case, that the magnitude of the reticulocyte response is governed directly by the extent of hyperplasia of the bone marrow during relapse, and the rate of the reticulocyte response directly by the dosage of the active principle in liver.

These more or less preliminary points having been discussed, one may now turn to a consideration of the bearing of the observations on the institution of a method for determining the potency of liver extracts. In the light of later developments, the observations on liver extract, by feeding, may be now regarded as being of a preparatory nature and not worthy of discussion at any length. A point, however, may be singled out for notice. The minimum dose of the extract capable of eliciting a response when given to the diseased fowl by mouth would appear to be in the neighborhood of from one-fourth to one-half phial

6 McGowan Brit M J 2 204, 1930

7 Riddle, M C Pernicious Anemia, Arch Int Med 46 417 (Sept) 1930

daily Proportionately, therefore, to the dose required in man,⁸ this is very large As the extract, as will be discussed immediately, shows itself to be very active when injected intraperitoneally, it seems probable that the explanation of its weak action when given by mouth is that it is not easily absorbed⁹ from the intestine of the fowl

In discussing now the experiments with intraperitoneal inoculation, as the cases in which iron was administered in addition to the liver extract do not differ materially from those in which liver extract was used alone, there appears to be no need for considering them separately A survey of the results, therefore, would seem to show that, in this case, the minimum dose of liver extracts potent in human cases (batches of liver extract 343, already mentioned) and capable of eliciting a response in the diseased fowl may be as low as (and may possibly be lower than) one-twentieth phial per day for white leghorn fowls of about 1,500 Gm in weight, under the conditions already specified as regards environment, food, dosage, etc. This figure, however, must be regarded as only a rough and approximate one, regard being had to the stage of the investigation and to the essential and specific nature of the disease It would seem best at present, moreover, to leave the results in this rough manner rather than to attempt to express them in the form of a possible fowl unit An increased number of observations and improved technic will doubtless supply more accurate results That, however, the accuracy obtained thus will not be available for the establishing of a unit such as exists, say, for insulin seems probable, the essentially different circumstances of the two cases being considered The problem is also complicated in another way, for there are no figures available for the potency of liver extract when injected intraperitoneally or otherwise into human beings with pernicious anemia

It is possible, however, that liver extract may be completely absorbed from the intestinal tract in human cases Under such circumstances, comparison in regard to the efficacy of liver extract in human and fowl conditions will be possible Lilly's liver extract is supplied in phials containing 4.5 Gm For a human being weighing, say, 140 pounds (63.5 Kg), the recognized daily dose is about 3 phials or 13.5 Gm The amount, therefore, of liver extract required per fourteen pounds of body weight would be 1.35 Gm For a fowl, the corresponding figure, based on the present results, would be 0.875 Gm When one considers that the 14 pounds and 3 phials are somewhat rough and arbitrary measurements, there is some justification, possibly slight, for considering the results obtained in the fowl and human being as being of the same order of magnitude

8 The dose recommended and generally used in human cases is 3 phials per day

9 It may possibly be destroyed in the intestine of the fowl

The present mode of estimation takes no cognizance of the possibility that the response to the reactive dosage may be due to a cumulative effect of the previous subactive doses. Such a storage effect has been shown to exist in human beings by Cohn, McMeekin and Minot¹⁰. It is not easy to see how a method could be devised to get round this difficulty, which after all is not of real importance, all the circumstances considered.

The important question of the method of obtaining diseased birds for observational purposes now arises for discussion. In the present instance the experimental fowls were obtained as cases occurring sporadically in the ordinary course of events in an ordinary commercial flock. In this case the incidence of the disease has been such that during the last three years 65 cases have occurred in an annual population of 800 fowls under 2 years of age. This is equivalent to about 2.7 per cent, or roughly 3 per cent, a figure which has already been employed. For many purposes this may be too infrequent an occurrence, and the question arises whether the number of cases cannot be augmented.

It seems practically certain that the great majority of cases of pernicious anemia in the fowl are caused by infestation by the tapeworm, *Davaanea proglottina*. It would be possible, therefore, to procure specimens by the feeding of fowls artificially with garden slugs, which act as the intermediate host and bearers of the cysticercoids of this tapeworm. Such experimental infestation has been carried out by Sawyer and Hamilton,¹¹ among others. This proceeding, however, would involve considerable labor and—as only a fraction of the fowls infected with *Davaanea proglottina* develop the anemia—much disappointment. It would seem preferable, therefore, to employ some scheme based on what is known of the natural occurrence of this parasitic infection. The following would seem to meet the case. If fowls known to be hosts of *Davaanea proglottina* were made to live with garden slugs in a confined area of a nature suitable (as regards the presence of vegetation, dampness, stones for protection, etc.) for the multiplication, development, etc., of the garden slug, this would seem to provide opportunities for intensified infestation. Under such circumstances, one would expect an increased supply of suitable cases of anemia.

CONCLUSIONS

A method for the quantitative determination of the potency of liver extracts by means of fowls suffering from pernicious anemia is described.

10 Cohn, McMeekin and Minot. J. Biol. Chem. **87** 1A, 1930.

11 Sawyer and Hamilton. West Washington Station Bull. 10-W, 1928, p. 43.

In substance, it consists of the injection intraperitoneally, twice daily over a period of time, of increasing small doses of the extract, until a dose is reached at which a "response" is obtained

The response consists in a sharply appearing and definite increase in the hemoglobin percentage and number of red blood cells

This response for the same sample of extract appears to be obtained at the same dosage, whatever the state of the marrow is, provided it is in a condition of hyperplasia and has not become aplastic

The response dose for fowls under the conditions specified in the text is in the neighborhood of one-twentieth phial or 0.225 Gm per day of the extracts employed

A method is suggested for the procuring of a more abundant supply of experimental cases

Dr Clowes, director of the Eli Lilly Laboratories, furnished me with supplies of liver extract Dr Marion B Richards prepared photographs and Mr Archibald Macdonald, M A, B Sc, supplied me with experimental fowls

ALBUMINURIA IN COLLEGE MEN

H S DIEHL, M D

AND

C A McKINLAY, M D

MINNEAPOLIS

Every practicing physician has observed that albuminuria may occur in certain persons who in other respects seem perfectly normal. Concerning the significance and the frequency of this finding, many and diverse opinions have been expressed in a voluminous literature on the subject. Writers have described different types of albuminuria and have assigned to them such names as adolescent, orthostatic, postural, lordotic and cyclic. These terms doubtless were intended to be qualifying, descriptive and helpful, but their multiplication has seemed to complicate rather than to clarify the problem.

Of these descriptive terms the one most widely used is orthostatic albuminuria, a name suggested by Teissier,¹ who in 1899 commented on the relation of changes in posture to the appearance and disappearance of albumin in the urine of certain persons. In 1910, Jehle² published his monograph on this condition and suggested the further qualifying term of lordotic albuminuria. Many writers before and since that time have observed that other conditions, such as muscular exertion, emotional disturbances, increased body temperature, malnutrition, certain drugs, etc., also may produce albuminuria in healthy persons and in experimental animals (Goetsky,³ Lewison, Freilich and Ragins⁴). Although the relationship of albuminuria to the erect, or orthostatic, position in certain cases and to lordotic posture in others has been definitely established, many persons with albuminuria show no evidence of lordosis, and many definitely crippled children do not show any higher percentage of albuminuria than children without lordosis. Furthermore, the difference in significance between these postural albuminurias and

¹ Submitted for publication, March 19, 1931

² From the Student's Health Service, University of Minnesota

³ A preliminary report of this study was presented in the Kidney Symposium at the University of Minnesota in July, 1930, and is being published with the proceedings of this symposium

1 Teissier, J L. Albuminurie de la station debout, albuminurie orthostatiques, *Semaine med* **19** 425, 1899

2 Jehle, B. Die lordatische Albuminuria, Berlin, Julius Springer, 1914

3 Goetsky, F K H. Zur Kenntnis der arthotischen Albuminuria, Diss., Berlin, 1910

4 Lewison, M, Freilich, E B., and Ragins, O B. Lordosis as a Cause of Postural Albuminuria, *Arch Int Med* **42** 440 (Sept) 1928

those that occur in other persons as a result of moderate exercise or emotional excitement or for no apparent cause is not clear. Hence in this report the use of the usual terms descriptive of types of albuminuria has been avoided.

This study of albuminuria in healthy young men is based on an analysis of the records of the physical examinations of 20,000 young men who entered the University of Minnesota as students between 1921 and 1930. In testing for albumin in the urine, the nitric acid test was used throughout, the reagent and the urine being layered in the test tube by means of a pipet.

INCIDENCE OF ALBUMINURIA

In this group of 20,000 young men, 1,065, or 5.32 per cent, were found to have albumin in the urine on the first examination, the amount of albumin varying from a trace, or one plus, in 79 per cent to a heavy cloud, three or four plus, in 6 per cent. Accurate comparison between these percentages and those reported by others is hardly possible, because the reagents that are used in performing tests for albumin differ in their ability to detect minimal amounts. Hill⁵ reported that 27.5 per cent of 417 men in a citizens' training camp showed albumin on a single examination when heat and acetic acid or sulphosalicylic acid were used, while only 3.3 per cent showed albumin when nitric acid was used. Furthermore, the observed incidence of albuminuria in most groups would be increased if several specimens of urine instead of a single specimen were examined. For example, last year at the University of Minnesota the health examinations showed albuminuria in 93 upper classmen, of this number 22 per cent had had albuminuria at the time of their entrance examinations, while 78 per cent had been free from albumin in the urine at this time. In general, however, the reported incidence of albuminuria as shown by the nitric acid ring test performed on a single specimen of urine varies from 3 to 16 per cent, with from 5 to 7 per cent being the most common.

Reexamination of Students with Albuminuria—Of these 1,065 students who showed albuminuria at the time of the entrance examination, 606 were reexamined by the Student's Health Service. Most of the others elected to go to private physicians for further study, while some dropped out of the university before the reexamination was made. It was the intention of the department to examine several specimens of urine, collected in the morning and in the evening, from each student who had shown albumin on the first examination, and in most cases this was done, a few students, however, failed to present additional specimens of urine for examination after having received one negative report. The results of these subsequent examinations are shown in table 1.

5 Hill, L. C. Febrile Albuminuria, *Quart J Med* 22:305 (Jan) 1929.

As will be seen from table 1, two thirds of the students who showed albuminuria at the time of the entrance examinations subsequently failed to show this condition, this is the group with so-called transitory albuminuria. Thirteen per cent had occasional albuminuria, most specimens being free from albumin, but more than one showing it. Twelve per cent had persistent albuminuria, all or nearly all specimens being positive for albumin, but without other evidences, at least convincing ones, of renal damage. Six and one-half per cent showed evidences of what was probably kidney disease. In this group with so-called "probably kidney disease" were placed those students who showed rather definite evidence of renal damage, as indicated by a considerable number or a

TABLE 1—*Reclassification of Group with Albuminuria, Six Hundred and Sixty Students Reexamined*

Group	Percentage of Original Albuminuric Group	Percentage of Total Student Body (Calculated)
Transitory albuminuria	66.2	3.6
Occasional albuminuria	13.09	0.7
Persistent albuminuria	11.8	0.6
Probably kidney disease	6.5	0.3

TABLE 2—*Quantity of Albumin in Relation to Its Persistence*

Quantity of Albumin on First Examination	Percentage of Final Classification		
	Transitory Albuminuria	Occasional or Persistent Albuminuria	Kidney Disease
Trace or +	74.6	25.2	2.1
++	52.9	36.8	10.3
+++	47.6	52.4	0.0
++++	6.3	75.0	18.7

persistence of leukocytes or blood cells or both in the sediment, the presence of a significant number of casts, a fixation of the specific gravity, inability on the part of the kidney to concentrate the urine or a diminished excretion of phenolsulphonphthalein. Most of the students in this group were studied by members of the Student's Health Service staff, but certain ones were under the care of private physicians, whose diagnoses of nephritis were accepted for this study.

The reclassification here used, of course, is an arbitrary one and only relatively accurate, for if a larger number of specimens had been examined, certain cases undoubtedly would have fallen into groups other than the ones in which they are now placed. The calculated percentages of the several classes of albuminuria show that in the student body as a whole albuminuria, except that which is transitory, is of infrequent occurrence.

PERSISTENCE OF ALBUMIN IN THE URINE

In this series there is a distinct relationship, as shown in table 2, between the amount of albumin reported on the first examination and its persistence on subsequent examinations, approximately three quarters of the students whose urines on entrance showed amounts of albumin reported as a trace or one plus later were classified as having transitory albuminuria, while only 6 per cent of those who had a four plus grade of albuminuria on the first examination were later free from albumin

FACTORS RELATED TO THE OCCURRENCE OF ALBUMINURIA

As there is still considerable lack of information regarding the cause, the significance and the relationships of albuminuria in healthy persons, an analysis of certain physiologic data recorded for students with and without albuminuria has been made. For purposes of comparison in making this analysis, the following groups were set up

1 The normal or control group, consisting of students in whose urines no albumin was discovered at the time of the entrance physical examination. Except for the last two years of the study, each one of the students in the control group was examined just before or just after a student with albuminuria. During the last two years the entire group of normals served as controls, but in computing the final percentages the results were weighed so as to have the same relation to the number of cases in the earlier years as obtained for the groups with albuminuria

2 The group with transitory albuminuria, consisting of those students whose original examinations showed albuminuria, but whose urines on subsequent examinations were always free from albumin

3 The group with persistent or occasional albuminuria, consisting of those students who were found on several occasions to have albuminuria and yet showed no definite evidence of kidney disease

4 The group with kidney disease, previously described. Although an effort was made to exclude those whose cases were essentially vascular, the group probably includes students with various types of renal damage

Age—As shown in chart 1, the proportion of students who show albuminuria decreases progressively with age. Calvin, Isaacs and Meyer,⁶ quoting Lauener, reported an increase in the incidence of albuminuria from childhood up to the age of 16 years. From this peak, which apparently occurs in the teens, there is a rapid decline in the incidence of the condition with advancing years to the group 30 years of age and over. The work of Sydenstricker and Britten⁷ shows that

6 Calvin, J. K., Isaacs, Bertha L., and Meyer, Jacob. Albuminuria in Children, *J. A. M. A.* **86** 182 (June 12) 1926

7 Sydenstricker, Edgar, and Britten, R. H. The Physical Impairments of Adult Life. General Results of a Statistical Study of Medical Examinations by the Life Extension Institute of 100,924 White Male Life Insurance Policy Holders Since 1921, *Am. J. Hyg.* **11** 73 (Jan.) 1930

after the age of 40 an increase in the incidence of albuminuria again occurs, being progressive with age up to 70 and over

Weight-Height-Age Percentage (chart 2) —The weight-height-age percentage here used represents the relationship of the individual student's weight to the standard, or average, weight for his age and height, as given in the medico-actuarial tables. The greater incidence of albuminuria among students of lighter weights is clearly shown in chart 2. The greater proportion of underweight students in the groups having the more persistent types of albuminuria and the smaller proportion of

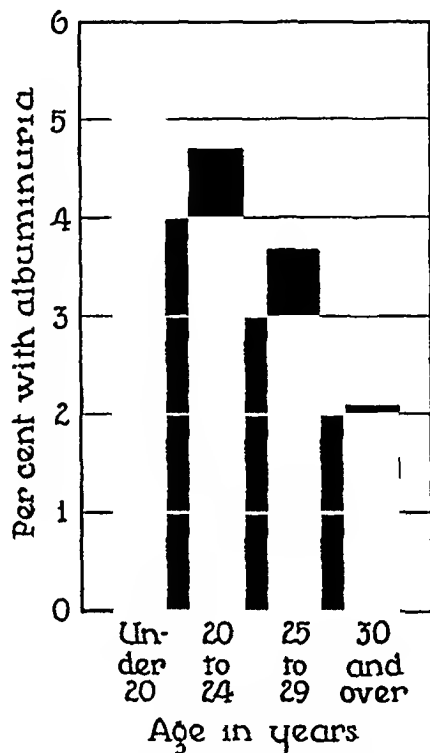


Chart 1 —Albuminuria and age

overweight students in those groups are evidence of the close relationship of body build not only to the occurrence, but also to the persistence, of albumin in the urine.

Pulse Rate —It is frequently stated that many persons who show albuminuria tend to be of a so-called high-strung, neurotic temperament. The striking increase in the incidence of albuminuria from 0.7 per cent in the students with pulse rates below 60 per minute to 18 per cent in those with pulse rates of 120 or over per minute lends remarkable support to this view. There is, however, no clear relationship between the pulse rate and the persistence of albumin in the urine. In fact, the groups with kidney disease and with persistent albuminuria show more uniform pulse rates than even the normal group.

Systolic Blood Pressure —The percentage incidence of albuminuria is surprisingly uniform at the various levels of systolic blood pressure.

(chart 4) There is also no tendency for hypertension to appear in any of the albuminuric groups except the group with kidney disease

Diastolic Blood Pressure—With the diastolic pressure, as with the systolic, there is no relationship between the level of the pressure

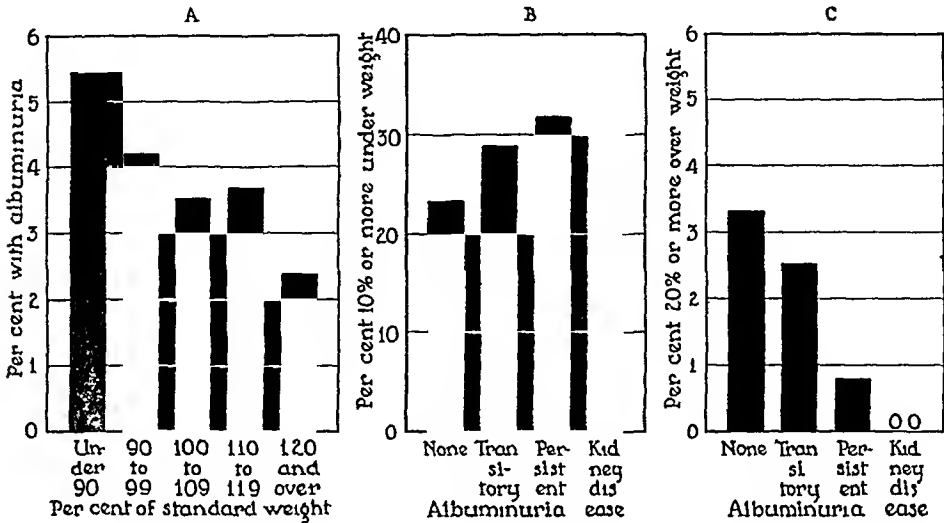


Chart 2—Albuminuria and weight *A*, incidence of albuminuria in various weight groups, *B*, underweights in the normal group and the several albuminuric groups, *C*, overweights in the normal group and the several albuminuric groups. In *A*, the standards used for weight, according to age and height, were taken from the medico-actuarial tables in general use

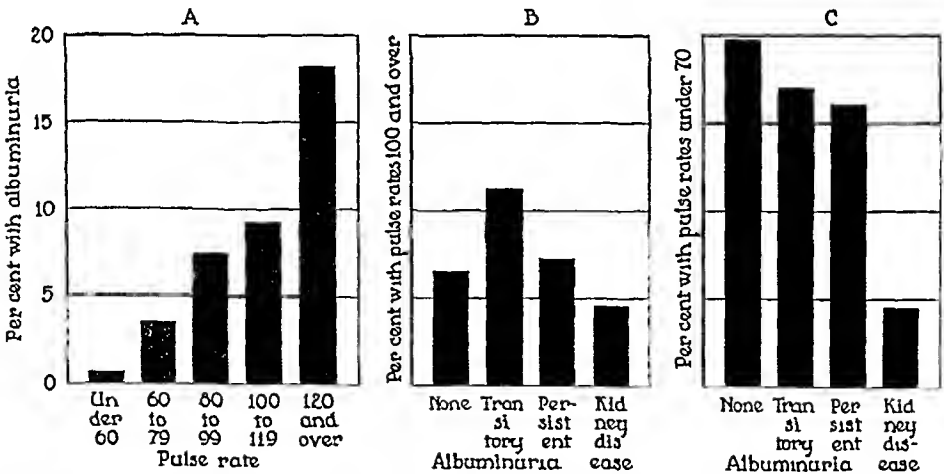


Chart 3—Albuminuria and pulse rate *A*, incidence of albuminuria in various pulse rate groups, *B*, rapid pulse rates in the normal group and the several albuminuric groups, *C*, slow pulse rates in the normal group and the several albuminuric groups

and the incidence of albuminuria (chart 5) The increase of diastolic pressure in the group with kidney disease corresponds to the increase in systolic pressure The progressively greater proportion of low diastolic

pressures in the several albuminuric groups suggests a relationship between albuminuria and the tonus of the circulatory system

Scarlet Fever—Past histories of those diseases thought most likely to be related to renal damage were compared for the normal group and the albuminuric groups. Scarlet fever (chart 6) had occurred with only a slightly greater frequency in the group with albuminuria than in the group without albuminuria. A greater percentage of students with the more persistent types of albuminuria gave histories of having had scarlet fever, but the differences between the groups were not sufficiently great to be statistically significant.

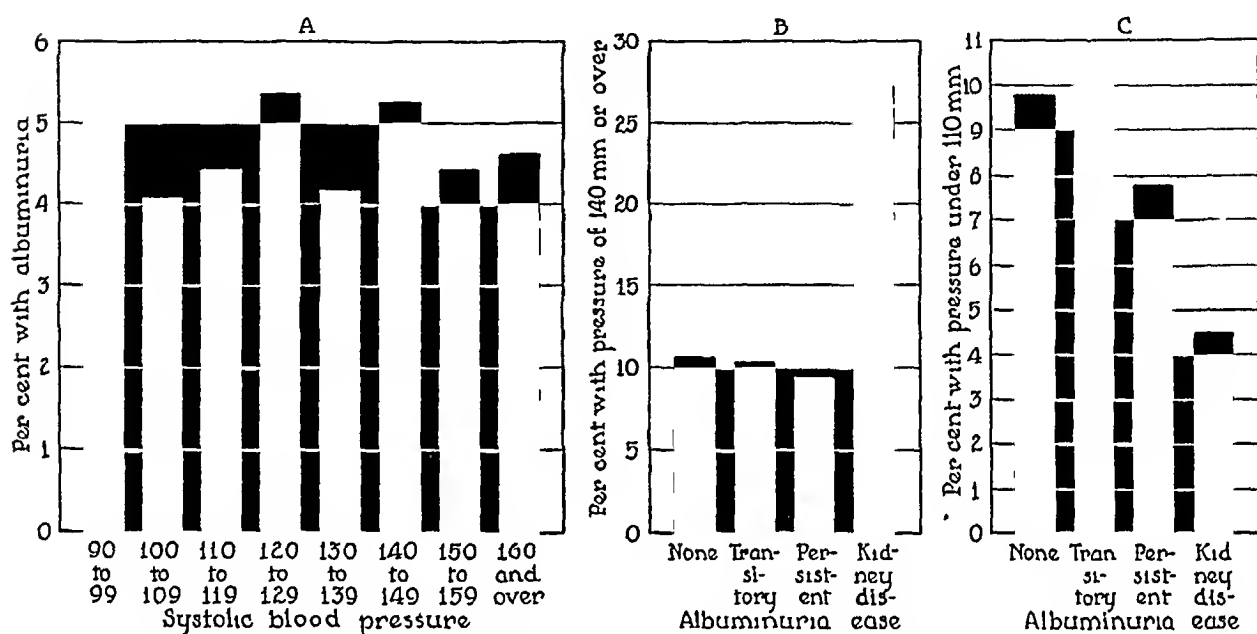


Chart 4—Albuminuria and systolic blood pressure. *A*, incidence of albuminuria in various blood pressure groups, *B*, high systolic pressures in the normal group and the various albuminuric groups, *C*, low systolic pressures in the normal group and the several albuminuric groups.

Diphtheria—Since diphtheria may cause a nephrosis, the incidence of diphtheria in the several albuminuric groups is compared in chart 6, but no relationship between these conditions is apparent.

Rheumatism—Although a history of rheumatism without further qualification is inexact, the term rheumatism has been used for comparative purposes as indicative of rheumatic fever, absorption from a focus of infection or some similar condition. Although the history of this condition was given infrequently (chart 6), the incidence is greater in the group with albuminuria and there is a steplike increase in the incidence of rheumatism from the group with no albuminuria to those with transient and persistent albuminuria and renal damage. This relationship, although not frequently emphasized, is not surprising in view of the etiologic relationship between glomerular nephritis and rheumatic conditions.

Colds—The entrance physical examination blank contains a question as to whether the student is subject to “frequent attacks of cold.” Since the term “frequent attacks” is not accurately defined, there is a considerable possibility of inaccuracy in these replies, but in a large group they probably are fairly satisfactory for comparative purposes. As shown in chart 6, there is a significantly greater incidence of “frequent colds” among the students who have albumin in the urine than among those in the control group. There is also a distinct relationship between the persistence of albumin in the urine and the history of frequent colds. A possible reason for this relationship may be that many persons who are subject to repeated colds have chronic sinus infections with recurrent acute or subacute manifestations.

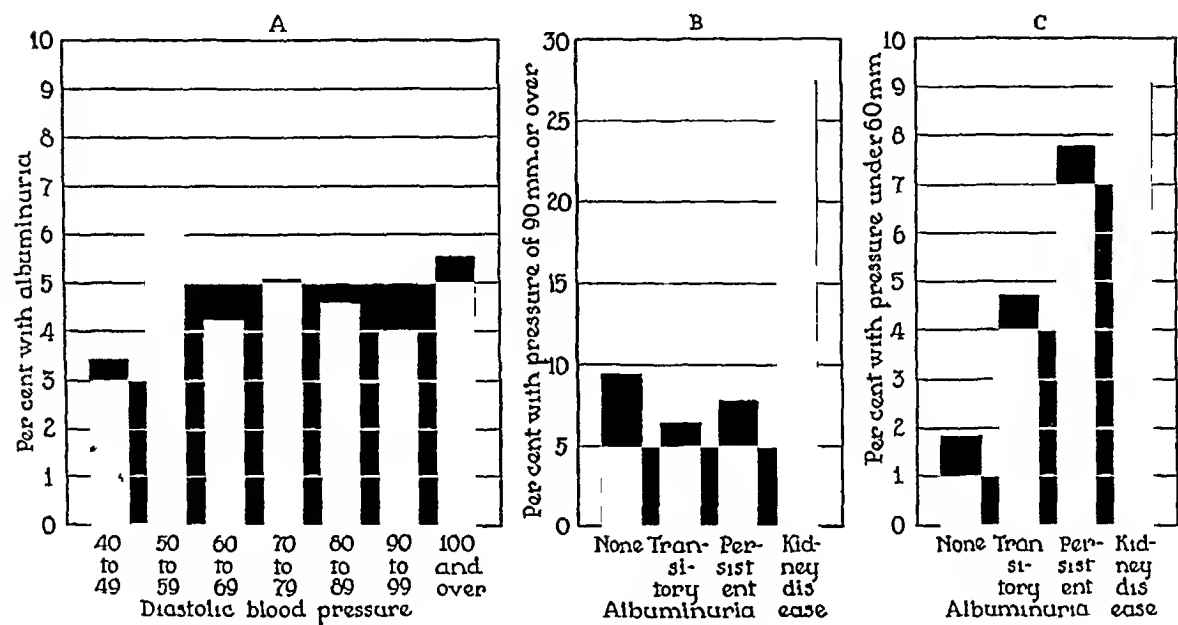


Chart 5—Albuminuria and diastolic blood pressure. *A*, incidence of albuminuria in various blood pressure groups, *B*, high diastolic pressures in the normal group and the several albuminuric groups, *C*, low diastolic pressures in the normal group and the several albuminuric groups.

Tonsillitis—The replies to the question on the history blank as to “frequent attacks of tonsillitis” are subject to the same inaccuracies and limitations as pertain to those concerning colds. The lack of relationship (chart 6) between albuminuria and a history of tonsillitis is surprising in view of clinical experience, but in this study it has been impossible to demonstrate any relationship.

Abnormal Tonsils—The examinations of the nose and throat on which these records concerning the tonsils are based were made by otolaryngologists. Various terms were used by them to describe the conditions of the tonsils, but for the purpose of this analysis those

conditions that seemed to have pathologic significance were grouped together and called "abnormal tonsils." Chart 6 shows a slight relationship, although not a very significant one, between normal tonsils and the occurrence of albumin in the urine. There is, however, no relationship between the persistence of albumin and the condition of the tonsils. This agrees with Ashburn's⁸ observation on West Point cadets, which he interprets as indicating that in his series there was

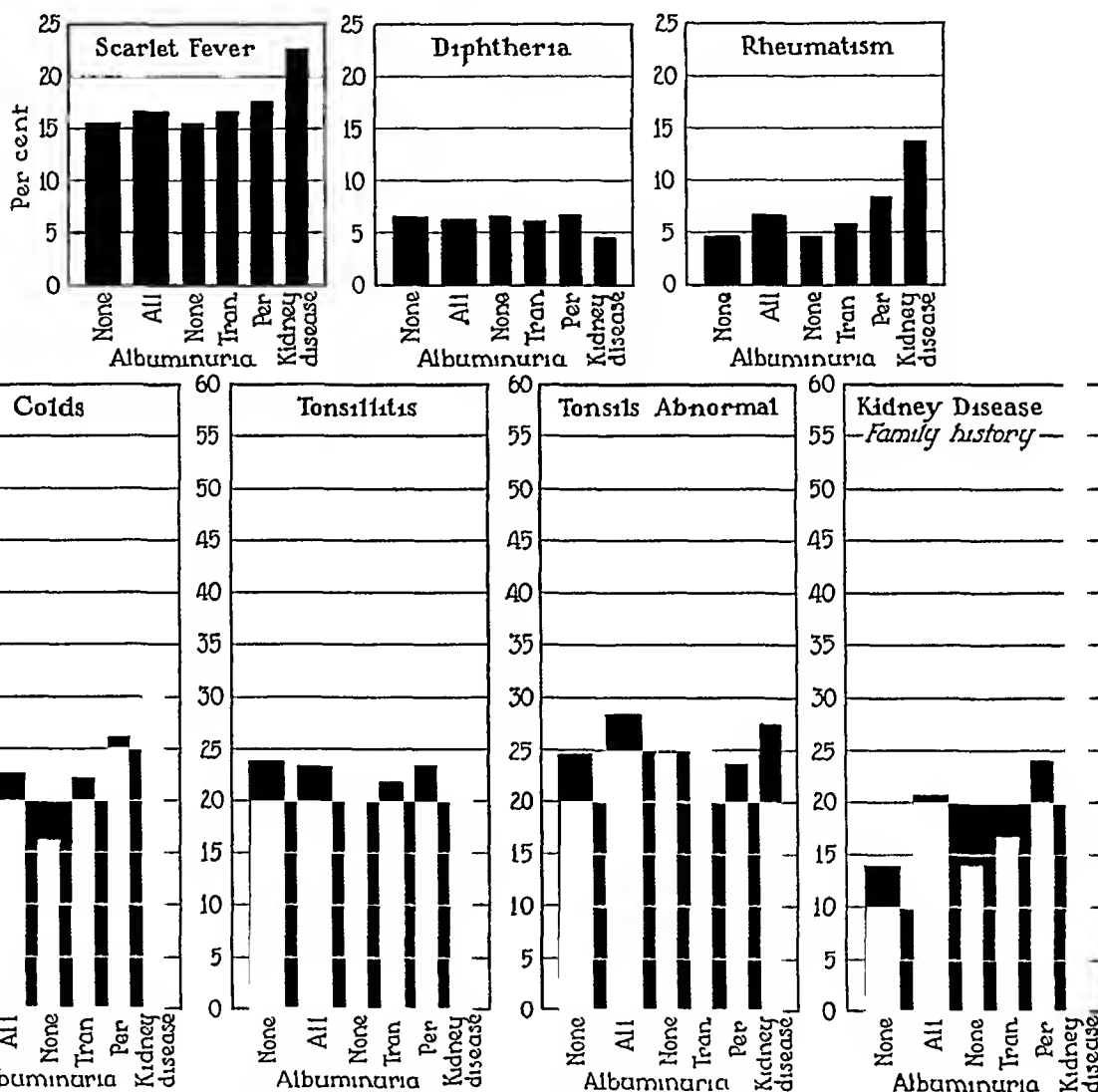


Chart 6—Albuminuria and past illnesses

nothing, not even in the results of tonsillectomies, to indicate that tonsillar infection was a causative factor in albuminuria.

Family History of Kidney Disease—During the more recent years of this study, information concerning the family histories of various diseases has been obtained. This "family history" refers not only

⁸ Ashburn, P. M. An Epidemic of Albuminuria, J. A. M. A 90 535 (Feb 18) 1928

to the immediate family, but also to grandparents and to uncles and aunts. One of the items about which inquiry is made in the family history is "kidney trouble." An analysis of these histories (chart 6) shows that students with albuminuria gave family histories of "kidney trouble" with distinctly and significantly greater frequency than the students who had no albuminuria. There is also a distinct, although not so positive, relationship between the persistence of albumin in the urine and the family history of "kidney trouble." This relationship between the family history of "kidney trouble" and albuminuria, although apparently quite definite for this group, might not be so striking if it were possible to eliminate from the group said to have kidney disease those adults whose disease was primarily vascular. However, we have found a less definite relationship between the blood pressures of the students and family histories of hypertension than between albuminuria and family histories of kidney disease.

COMMENT

The significance of albuminuria unassociated with other evidences of renal damage in young adults is an important question concerning which there is a distinct lack of agreement among physicians. Some writers believe that all or nearly all of the cases of albuminuria are, or have been, associated with some renal damage. Others believe that the condition is of little or no significance, and that in most persons albuminuria is consistent with the prospect of a perfectly normal life. This study, while not answering the all-important question as to the significance of albuminuria, shows certain interesting and significant relationships.

The slight statures, the rapid pulse rates, the lower diastolic blood pressures, the indications of a familial trait and even the greater susceptibility to infections among the students with albuminuria suggest that what certain writers have called a "constitutional inferiority" may be related to albuminuria in this group. In fact, after reviewing the evidence presented in the literature, Fishberg⁹ concluded that "the constitutional factor is a very important one in determining the occurrence of albuminuria."

The higher blood pressure, both systolic and diastolic, in the group with kidney disease is just what would be expected. The slight, though hardly significant, upward tendency of the blood pressures of the other albuminuric groups could be caused by the inclusion in these groups of either some students with early primary hypertension or some with early renal damage, not yet recognizable by our methods of examination.

⁹ Fishberg, A. M. *Hypertension and Nephritis*, Philadelphia: Lea & Febiger, 1930, p. 235.

As to possible contributory factors in the etiology of albuminuria, one finds a marked relationship between albuminuria, frequent attacks of "colds" and a family history of kidney disease, and a slight, though definite, relationship between albuminuria and a history of rheumatism or of scarlet fever. The possible interrelationship of these several conditions that seem related to albuminuria will be the subject of later investigation.

The definite steplike progression in the incidence of several of these conditions from the groups without albuminuria through those with transient and persistent albuminuria to the ones with kidney disease strongly suggests that either there are persons with unrecognized nephritis in these groups with transient, occasional and persistent albuminuria, or there are some physical or physiologic peculiarities in certain persons that tend toward the development of albuminuria and kidney disease. In either case it is doubtless well to be conservative in one's judgments as to the significance or lack of significance of occasional findings of albumin in the urine, even though with present methods one is unable to discover other evidences of renal damage.

SUMMARY

1 Of 20,000 male students at the University of Minnesota, 5.32 per cent showed albumin in the urine on the examination of a single specimen with the nitric acid ring test.

2 On reexamination in 606 cases of albuminuria, 66.2 per cent showed albumin on only one examination, 13.1 per cent showed occasional albuminuria, 11.8 per cent showed persistent albuminuria, and 6.5 per cent gave evidence of what was probably kidney disease.

3 The calculated percentage of the total group that showed persistent albuminuria and probably kidney disease is so small that even though there may be some overlapping in the groups, it is evident that kidney disease is a rare condition in young adults.

4 No significant relationships were found between albuminuria and systolic or diastolic blood pressure, a history of diphtheria or of tonsillitis or tonsils that on examination appeared abnormal.

5 Definitely positive and apparently significant relationships exist between albuminuria and weight, pulse rate, a history of rheumatism, "frequent colds" and a family history of kidney disease.

THE ACIDOSIS OF NEPHRITIS

ITS CLINICAL SIGNIFICANCE *

A P BRIGGS, M D

ST LOUIS

In various types of chronic nephritis there develops a disturbance of the inorganic metabolism that is dependent, in part at least, on impairment of renal function. Sooner or later this disturbance is complicated to a variable degree by any or several of such concomitant disturbances as loss of appetite, vomiting, albuminuria and edema. On account of the discouraging number of variables encountered in clinical nephritis, Atchley and Benedict¹ studied the influence of obliteration of renal function in dogs by means of ligation of both ureters, they expressed the belief that they had produced the picture of uncomplicated renal insufficiency.

The plan of the present contribution was to study the inorganic disturbance in cases of clinical nephritis in which complications were relatively slight. Observations were made over a period of three years during intervals when disturbing influences for the most part seemed negligible. Appetite was not infrequently poor, but there was no vomiting except as stated. Although albuminuria was present to a variable degree, the serum protein was maintained above 5 per cent, and edema, if present on the patient's entrance to the hospital, had responded to treatment for an underlying cardiac disturbance.

CLINICAL MATERIAL

The type of renal disease in most of the cases studied was arteriosclerotic nephritis, according to the classification of Addis². The majority of the patients were middle aged or elderly persons with a history of shortness of breath and swelling of the ankles or lower extremities appearing shortly before entrance to the hospital. Examination in this group revealed hypertension, albuminuric retinitis and signs of heart failure. With rest in bed and moderate doses of digitalis there were prompt symptomatic improvement and disappearance of edema.

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* From the Department of Internal Medicine, St. Louis University School of Medicine

1 Atchley, Dana W., and Benedict, Ethel M. The Distribution of Electrolytes in Dogs Following Ligation of Both Ureters, *J Biol Chem* **73** 1 (May) 1927

2 Addis, T. The Renal Lesion in Bright's Disease, *Am J M Sc* **176** 617 (Nov) 1928

The patient in case 66997 was nauseated and vomited occasionally on the day of entrance, influences of which are seen in the analysis of serum obtained the following day. He died a few days later. In case 67676 there had been some nausea and vomiting associated with an infection of the upper respiratory tract a few days before blood was taken for analysis.

In cases 67156 and 68497 the patients were younger persons with high blood pressure and similarly advanced renal impairment. The former patient had marked thickening of palpable arteries and advanced retinal sclerosis, the latter had no perceptible thickening of palpable arteries and only beginning retinal sclerosis. These findings were of special interest in connection with the difference in the tolerance of the patients for mineral acid and the question of uremia. In the latter case there was a questionable diagnosis of hemorrhagic nephritis on account of persistent slight hematuria.

Case 67643, that of a woman aged 22, was one of rapidly progressing malignant hypertension.

Case 65255 was one of subacute nephritis with hematuria and slight edema.

METHODS

Except during metabolism tests or when otherwise indicated, the subjects received the regular house diet.

Blood was taken for analysis about four hours after the morning meal. From 30 to 40 cc was drawn with minimal stasis into an oil-coated syringe, and discharged under oil into a 50 cc centrifuge tube. The carbon dioxide content was determined promptly after centrifugation with an original Van Slyke apparatus. The serum was then removed with a pipet. Duplicate samples of 1 cc each were measured into 50 cc pyrex beakers for determination of the total base, a 0.5 cc sample was transferred to a 50 cc volumetric flask for determination of protein nitrogen, 2 cc was saved for emergency, the rest was precipitated with trichloroacetic acid for determination of phosphoric, sulphuric and hydrochloric acids and of nonprotein nitrogen. In a few instances samples of serum were taken before exposure to air for colorimetric determination of p_H . Determinations of the various acids were not made in duplicate and were repeated only in case of accident or doubtful result.

Urine was collected in large stoppered bottles containing chloroform as a preservative.

Chemical Technic—The total fixed base was determined for serum by a technic essentially that of Stadie and Ross³. It was observed that results were low if any appreciable amount of carbon remained after evaporating the digest to dryness, presumably because some sulphate was converted to oxide and part of this to silicate during the ignition, and also that numerous additions of nitric acid were required to obtain complete digestion when the procedure was carried out as directed by Stadie. Accordingly, the following technic, which gave good digestion and required little attention, was adopted. To the sample of serum, 0.5 cc of

3 Stadie, William C, and Ross, Effie C. A Micro-Method for the Determination of Base in Blood and Serum and Other Biological Materials, *J Biol Chem* 65 735 (Oct) 1925

sulphuric acid and 10 cc of nitric acid were added, the beaker was covered with a watch glass, and the mixture was boiled gently for six hours. The cover glass was then removed, the digest evaporated to dryness, and the determination completed according to the Stadie technic. Addition of potassium dihydrogen phosphate in quantities up to the equivalent of 0.1 mg of phosphorus to serum or to samples of solutions of known fixed base had no influence on the result. Phosphorus was, therefore, not removed from serum, but the correction for base bound as metaphosphate in the ignited residue was calculated from the phosphate determination. The value given for serum fixed base is the average of duplicate determinations that checked within 4 milliequivalents. Fixed base in urine was determined by a similar technic after removal of phosphate with ferric iron. Serum chloride, in the work on case 68497, was determined by the method of Wilson,⁴ and in the other cases by a similar titration on trichloroacetic filtrate. Chloride in urine was determined as in the Wilson method. Sulphate in urine was determined by a benzidine titration as in the method of Fiske.⁵ However, phosphate was removed by centrifugation after precipitation with calcium acetate, and the benzidine sulphate was likewise separated and washed by centrifugation. Sulphate in trichloroacetic filtrate was precipitated as in the method of Wakefield,⁶ but the color used for comparison was that of Yoshimatsu.⁷ In my hands this color, developed with ammonia and iodine, has proved to be more intense and stable and more quickly developed than the color developed with peroxide and ferric iron which was used by Wakefield. In the earlier part of this study, serum sulphate was determined by the method of Denis and Reed.⁸ The phosphate in trichloroacetic filtrate and urine was determined colorimetrically as in the Briggs method.⁹ The reducing agent employed was a solution containing 1 per cent hydroquinone and 5 per cent sodium bisulphite. For each 0.1 mg of phosphorus anticipated 1 cc of the reducing agent was added. A valence of 18 was assumed for phosphate in both serum and urine as in the study of Gamble and his associates.¹⁰ Serum base bound as bicarbonate was calculated by means of the factor 0.423, used by Atchley and Benedict.¹ The method used for the determination of sodium in urine was that of Kramer and Gittleman.¹¹ Ammonia in urine was determined by the permittit

4 Wilson, D. Wright, and Ball, Eric G. A Study of the Estimation of Chloride in Blood and Serum, *J Biol Chem* **79** 221 (Sept.) 1928

5 Fiske, Cyrus H. The Determination of Inorganic Sulfate, Total Sulfate, and Total Sulfur in Urine by the Benzidine Method, *J Biol Chem* **47** 59 (June) 1921

6 Wakefield, E. G. The Colorimetric Determination of Total and Inorganic Sulfates in Blood Serum, Urine, and Other Body Fluids, *J Biol Chem* **81** 713 (March) 1929

7 Yoshimatsu, S. Colorimetric Methods for Determining Sulfate in Urine, Blood, and Milk, *Tohoku J Exper Med* **7** 119 (April) 1926

8 Denis, W., and Reed, Lucille. Methods for the Determination of Some of the Non-Protein Sulfur Compounds of Blood, *J Biol Chem* **71** 191 (Dec) 1926

9 Briggs, A. P. A Modification of the Bell-Doisy Phosphate Method, *J Biol Chem* **53** 13 (July) 1922

10 Gamble, James L., Blackfan, Kenneth D., and Hamilton, Bengt. A Study of the Diuretic Action of Acid Producing Salts, *J Clin Investigation* **1** 359 (April) 1925

11 Kramer, Benjamin, and Gittleman, I. An Iodometric Method for the Determination of Sodium in Small Amounts of Serum, *J Biol Chem* **62** 353 (Dec) 1925

method of Folin and Bell¹² Proximate p_H determinations were made on urine as directed by Clark,¹³ and on serum by the method of Cullen¹⁴ Protein nitrogen in serum was determined colorimetrically, acacia being used for a protective colloid as suggested by Chiles¹⁵ Nonprotein nitrogen in trichloroacetic filtrate was determined similarly The factor 2.36 was used as by Atchley and Benedict¹⁶ for calculating base bound by protein Creatinine in urine was determined by the Folin method¹⁷

SERUM ACID AND BASE

The condition of the electrolytes, as shown in table 1, is seen to be almost similar to that observed by Atchley and Benedict¹ in the early stage of kidney block produced by ligation of both ureters The levels of phosphate and sulphate are elevated, and this change is approximately balanced by a drop in bicarbonate with no characteristic change in chloride The level of serum fixed base in these patients, however, is slightly lower than the average normal value which was unchanged by experimental kidney block in the study of Atchley and Benedict¹

Studies of unselected cases of clinical nephritis usually show wide fluctuations in the level of chloride, with low values more common than high Inspection of the tables and protocols of the studies of Bulger, Peters and their co-workers¹⁸ and Hartmann and Darrow¹⁹ and of those of the study of Atchley and Benedict,¹⁶ which has just appeared,

12 Folin, Otto, and Bell, Richard D Applications of a New Reagent for the Separation of Ammonia I The Colorimetric Determination of Ammonia in Urine, *J Biol Chem* **29** 329, 1917

13 Clark, W Mansfield The Determination of Hydrogen Ions, ed 2, Baltimore, Williams & Wilkins, 1923

14 Cullen, Glenn E The Colorimetric Determination of the Hydrogen Ion Concentration of Blood Plasma, *J Biol Chem* **52** 501 (June) 1922

15 Chiles, H M Direct Nesslerization of Kjeldahl Digestions, *J Am Chem Soc* **50** 217, 1928

16 Atchley, Dana W, and Benedict, Ethel M Serum Electrolyte Studies in Normal and Pathological Conditions Pneumonia, Renal Edema, Cardiac Edema, Uremic and Diabetic Acidosis, *J Clin Investigation* **9** 265 (Oct) 1930

17 Folin, Otto On the Determination of Creatinine and Creatine in Urine, *J Biol Chem* **17** 469, 1914

18 Bulger, H A, Peters, John P, Eisenman, A J, and Lee, Carter Total Acid-Base Equilibrium of Plasma in Health and Disease VII Factors Causing Acidosis in Chronic Nephritis A Preliminary Report, *J Clin Investigation* **2** 213 (Feb) 1926 Peters, John P, Wakeman, A Maurice, Eisenman, Anna J, and Lee, Carter Total Acid-Base Equilibrium of Plasma in Health and Disease X The Acidosis of Nephritis, *ibid* **6** 517 (Feb) 1929

19 Hartmann, Alexis F, and Darrow, Dan C Chemical Changes Occurring in the Body as a Result of Certain Diseases in Infants and Children II Acute Hemorrhagic Nephritis, Subacute Nephritis, Severe Chronic Nephritis *J Clin Investigation* **6** 127 (Aug) 1928

TABLE 1—Condition of Electrolytes in Blood Serum in Nephritis*

Case and Date	NPN	pH	HCO ₃ PO ₄	SO ₄	Cl	Pro tem	Total Acid	Total Base	Difference Between Base and Acid	Remarks
M P 62367										
2/ 1/1928	91		18.1	3.6	3.0	102.5	14.8	142.0	146.1	4.1
2/11/1928	89		21.6	3.8	2.7	100.0	14.9	142.9	145.9	3.0
2/24/1928	93		20.3	2.6	3.7	102.6	14.4	143.6	148.5	4.9
										High base diet since 2/11/1928
										CaCO ₃ , 6 Gm daily
L C 64392										
12/ 4/1928	67		19.9	3.7	1.6	104.1	14.9	144.2	150.2	6.0
12/29/1928	67		22.7	2.5	1.0	105.0	14.9	146.5	150.0	3.1
1/19/1929			20.3	3.6	2.2	102.6	15.3	144.0	147.3	3.3
2/ 4/1929	72		18.1	5.6	1.5	100.0	15.2	140.4	145.4	5.0
										SrCO ₃ , 6 Gm daily since 12/4/1928
										H ₃ PO ₄ test
B J 64838										
2/26/1929	105		17.5	4.4	4.6	104.8	14.6	145.9	150.4	4.5
3/ 4/1929	110		18.6	3.1	4.3	105.9	14.6	146.5	150.7	4.2
										CaCO ₃ , 6 Gm daily since 2/26/1929
3/ 9/1929	125		13.9	5.8	5.2	102.5	15.2	142.6	147.1	4.5
										H ₃ PO ₄ test
E S 65255										
5/27/1929	52		24.1	2.6	1.2	102.5	15.3	145.7	148.5	2.8
6/10/1929			22.8	2.4	1.3	105.0	15.5	147.0	152.4	5.4
J V 66997										
2/20/1930	121		19.5	5.0	5.3	98.0	12.8	140.6	143.8	3.2
										Recent vomiting
M P 66998										
3/29/1930	153		14.8	5.2	6.6	102.0	14.3	142.9	146.1	3.2
4/21/1930	154		18.6	1.9	3.6	102.4	16.2	142.7	147.5	4.8
										SrCO ₃ , 6 Gm daily since 3/29/1930
5/ 7/1930	150		18.6	2.9	4.0	104.0	13.6	143.3	148.6	5.3
										High base diet
E D 67024										
2/24/1930	105		17.6	3.2	3.4	104.1	14.9	143.2	148.5	5.3
3/13/1930	97		22.2	3.1	2.9	102.3	13.6	144.1	147.8	3.7
3/16/1930			14.1	2.7	7.2	103.0	14.7	141.7	147.0	5.3
4/ 1/1930	100		18.7	4.2	3.6	102.3	14.3	142.1	147.5	5.4
										High base diet (NH ₄) ₂ SO ₄ test
J L 67156										
3/19/1930	125	7.36	16.3	4.4	5.0	102.3	15.8	143.8	150.4	6.6
3/22/1930	124	7.24	13.3	7.0	5.2	102.0	15.3	142.7	145.9	3.2
4/25/1930	103	7.38	18.2	2.8	3.5	106.8	15.6	146.9	149.5	2.6
										H ₃ PO ₄ test
										SrCO ₃ , 6 Gm daily since 3/22/1930
5/14/1930	125		17.4	3.9	4.7	104.9	15.2	146.1	150.9	4.8
5/26/1930	167	7.28	13.9	4.8	6.6	108.2	16.6	150.1	154.7	4.6
6/12/1930	130		16.1	3.5	5.7	104.1	14.7	144.1	148.9	4.8
										Liver administration
D H 67506										
5/15/1930	62		18.6	3.1	1.2	103.6	16.8	145.4	148.7	3.3
6/ 3/1930		7.40	20.7	3.1	1.2	105.0	16.4	147.1	150.7	3.6
6/18/1930	59	7.28	16.1	2.8	5.0	107.1	17.1	148.0	151.6	3.6
										(NH ₄) ₂ SO ₄ test
L S 67643										
6/12/1930	66		22.8	3.0	2.0	99.3	15.7	142.8	146.1	3.3
										Recent vomiting
J S 67676										
8/ 2/1930	66		21.4	3.2	1.2	100.8	13.8	140.4	146.6	6.2
										Recent vomiting
E M 67985										
8/13/1930	52		25.8	2.5	0.9	104.0	16.8	150.0	155.4	5.4
8/22/1930			21.0	2.5	1.7	105.8	16.8	148.8	151.8	3.0
										(NH ₄) ₂ SO ₄ test
G F 68497										
10/ 9/1930	119	7.38	20.2	3.3	4.8	107.5	15.6	151.4	153.8	2.2
10/15/1930	121	7.20	14.5	3.7	9.2	104.7	18.3	150.4	154.0	3.6
11/15/1930	120		19.9	3.4	4.6	101.2	15.6	144.7	149.8	5.1
12/20/1930	118		21.0	2.2	2.1	104.0	16.1	145.4	150.2	4.8
										SrCO ₃ , 6 Gm daily since 11/15/1930
12/29/1930	108		21.4	3.8	4.0	99.1	15.5	143.8	145.5	1.7
1/ 8/1931	111		20.7	4.1	3.8	104.5	15.4	148.5	152.3	3.8
										Recent vomiting

* The figures for acids and bases represent milliequivalents per liter. Average values obtained by the same methods on patients without disturbance of inorganic metabolism are approximately as follows: HCO₃ = 27, Cl = 105, PO₄ = 1.8, SO₄ = 0.5, protein = 17.6, and total fixed base = 152.

shows an occasional level of chloride somewhat higher than normal, but associated with edema, a complication that was negligible in the present study. There is rather common association of a low chloride level with vomiting or with dehydration resulting from vomiting and diarrhea. In many of the reported cases with advanced functional impairment but without vomiting or edema, the chloride values were strictly normal, like those of the present study. It seems doubtful, then, that abnormal serum chloride values are characteristic of the disturbance resulting from impaired renal function.

There is a clear relation of phosphate and sulphate retention to renal insufficiency, as pointed out by Atchley and Benedict¹⁶. The level for serum protein is frequently lower than in the present study, but when low is associated with edema. The question of ketone acid retention raised by Peters and his co-workers¹⁸ seems to have been answered in the study of Atchley and Benedict¹⁶. In the present study there was no occasion to suspect a starvation or pancreatic ketosis, and it will be observed that the balance obtained between total acids and fixed base usually leaves little room for accumulated organic acid.

It should be added that the observations considered so far were fairly well indicated in the early study of Denis and Hobson,²⁰ who showed rising levels of sulphate and phosphate and depletion of the alkaline reserve associated with retention of nonprotein nitrogen and creatinine. A few high chloride values were associated with edema, the few low chloride values were obtained from moribund patients with a presumptive association of vomiting.

In the study of Denis and Hobson²⁰ the basic elements were determined separately, on account of inherent errors in the sodium method, the values for total fixed base, calculated from their results, probably are all too high. Still, except with patients in a moribund state and with chloride levels suggestive of vomiting, the values obtained for the basic elements were similar to those obtained for normal controls by the same methods. Fixed base depletion was not considered by these authors as a characteristic of advanced clinical nephritis. Subsequent work with improved technic has likewise failed to demonstrate serious depletion of serum fixed base to be such a characteristic. The studies of Peters et al.,¹⁸ and of Atchley and Benedict¹⁶ showed marked depression of the fixed base level to be consistently associated with vomiting, and in the study of Hartmann and Darrow¹⁹ the conspicuously low levels of fixed base were associated with dehydration due to vomiting and diarrhea. All of these authors

²⁰ Denis, W., and Hobson, S. A Study of the Inorganic Constituents of the Blood Serum in Nephritis, *J Biol Chem* **55** 183 (Feb) 1923

observed, however, that in cases in which extraneous causes for loss of fixed base appeared to be absent, the level of serum fixed base in chronic nephritis with functional impairment was usually at or slightly below the lower limit of normal fluctuation, they have concluded that this was due to some defect in the renal mechanism for the conservation of fixed base

In the present study, in which complicating disturbances were minimum, the level of serum fixed base was observed to be usually between 145 and 152 milliequivalents per liter, whereas the normal limits obtained by Atchley and Benedict¹⁶ were from 148 to 155. The levels in health and chronic nephritis are, therefore, so close together that their fluctuations overlap. About 1 milliequivalent of this discrepancy can be accounted for by the influence of a high phosphate and low protein content on serum calcium. A small balance of the discrepancy remains, which it seems might well be due to some renal defect in conservation of base. Much of the present study was concerned with the nature of this defect.

URINARY EXCRETION OF INORGANIC CONSTITUENTS

Examination of the urine in nephritis fails to show insufficient excretion of the inorganic acids. Boyd²¹ found that nephritic and normal children on the same diet excreted similar quantities of phosphoric acid. Gamble and his associates¹⁰ found that a nephritic and a normal child on the same diet excreted similar quantities of the various acids and total fixed base. Van Slyke and his co-workers²² found the titratable acid of the urine well maintained in nephritis until the terminal stage. Apparently the nonthreshold acids, *i. e.*, sulphuric and phosphoric, accumulate in the blood to an equilibrium level at which filtration or secretion per glomerulotubular unit of kidney remnant is sufficiently increased to maintain metabolic balance.

In considering the excretion of fixed base in nephritis we are not so much concerned with elimination as with conservation. Excess of any of the basic elements is thrown off by the intestine as well as by the kidney, so that retention of fixed base is not a problem in renal insufficiency. The question of conservation of fixed base, on the other hand, is of much interest, since many foodstuffs in the average diet contain more potential acid than base, *i. e.*, have an acid ash

21 Boyd, Gladys L., Courtney, Angelia M., and MacLachlan, Ida F. The Metabolism of Salts in Nephritis. I. Calcium and Phosphorus, *Am J Dis Child* 32:29 (July) 1926.

22 Van Slyke, D. D., Linder, G. C., Hiller, Alma, Leiter, L., and McIntosh, J. F. The Excretion of Ammonia and Titratable Acid in Nephritis, *J Clin Investigation* 2:255 (Feb) 1926.

(Sherman and Gettler²²), and the kidney carries the burden of excreting this excess acid with a minimum loss of fixed base

It is simple enough to suppose that the pathologic condition observed in usual types of chronic nephritis with renal insufficiency might lead to retention of the less diffusible acids, which depend on the kidney for excretion, but it is not so easy to understand why this same condition should lead to a waste of fixed base. That is to say in view of the prevailing conceptions of renal pathology and physiology if the damage to the kidney is primarily at the glomerulus, whether from a toxin of hemorrhagic nephritis or from the process of arteriosclerosis, one might expect, with decreased formation of glomerular fluid, as indicated by the studies of Rehberg²⁴ higher levels of various urinary constituents in the blood stream. On the other hand if damage to the tubule is the result of occlusion of the glomerular tuft, the nutrition and ability of any tubule to reabsorb vital constituents should be preserved in proportion to the circulation through the corresponding glomerulus and somewhat in proportion to the amount of glomerular fluid formed.

During the course of this study it has become obvious that many phases of the inorganic disturbance in nephritis are made clearer by a consideration of the probable difference between a nephritic and a normal subject with regard to the rate of flow of glomerular fluid through the tubules. Marshall²⁵ and Carr²⁶ have shown that diuresis produced by drinking distilled water makes the urine more alkaline. Excretion of inorganic acids is increased, but excretion of ammonia is unchanged. Diuresis therefore causes waste of more fixed base than acid. Apparently the increased rate of flow of glomerular fluid through the tubules affords less opportunity for modification by reabsorption of fixed base or enrichment with acid. The urine more closely resembles plasma in composition. In any of the ordinary types of chronic nephritis with impaired renal function the volume of urine is somewhat greater than normal especially at night. The situation is therefore, one in which an increased volume of urine passes through

23 Sherman, H. C., and Gettler, A. O. The Balance of Acid-forming and Base-forming Elements in Foods and Its Relation to Ammonia Metabolism. *J. Biol. Chem.* **11**:323, 1912.

24 Rehberg, Poul Brandt. Ueber die Bestimmung der Menge des Glomerulus-Filtrats mittels Kreatinin als Nierenfunktionsprüfung nebst einigen Bemerkungen über die Theorien der Harnbereitung, *Zentralbl. f. inn. Med.* **50** 367 (April 13) 1929.

25 Marshall, E. K., Jr. The Influence of Diuresis on the Elimination of Urea, Creatinine and Chlorides, *J. Pharmacol. & Exper. Therap.* **16**:141 (Oct) 1920.

26 Carr, A. D. The Effect of Water Diuresis on the Elimination of Certain Urinary Constituents, *J. Pharmacol. & Exper. Therap.* **18** 221 (Oct) 1921.

relatively few remaining tubules. The rate of flow through the tubules must be considerably increased. Starting at the other end of the process, it may be supposed that in each surviving renal unit a compensatory increased rate of formation of glomerular fluid occurs, although the total quantity of glomerular fluid as calculated by Rehbeig²⁴ is decreased. With increased rate of flow through the tubules, imperfect reabsorption of water and fixed base and, to a lesser extent, of chloride and other constituents of the glomerular fluid results. Since this compensatory diuresis is sustained day and night, evidence of slight depletion of fixed base in serum seems to be adequately accounted for.²⁷

Hartmann and Darlow¹⁹ suggested that the polyuria of chronic nephritis might in some way be related to the reduced level of serum fixed base. Atchley and Benedict¹⁶ expressed the belief that such a view lacks experimental proof, and pointed to the failure of diuresis to change the level of serum fixed base in a patient with cardiac disease and edema and good renal function. They observed later, nevertheless, that the fixed base level in a nephritic patient was reduced 5 milliequivalents by forcing fluids for one week. This result might be anticipated by a consideration of the probable difference in the rate of flow through the tubules of a patient with cardiac disease and those of a nephritic patient, for an increase in the volume of urine of any magnitude distributed among the hundreds of thousands of tubules of a normal renal apparatus would not be expected to create nearly so great an increased rate of flow as that produced by the few glomerulotubular units of a kidney remnant. A diuresis that caused excretion of little extra fixed base in the normal renal apparatus might result in the loss of a considerable quantity in the nephritic patient. Experimental support for this assertion is offered in the study of case 68497, table 7.

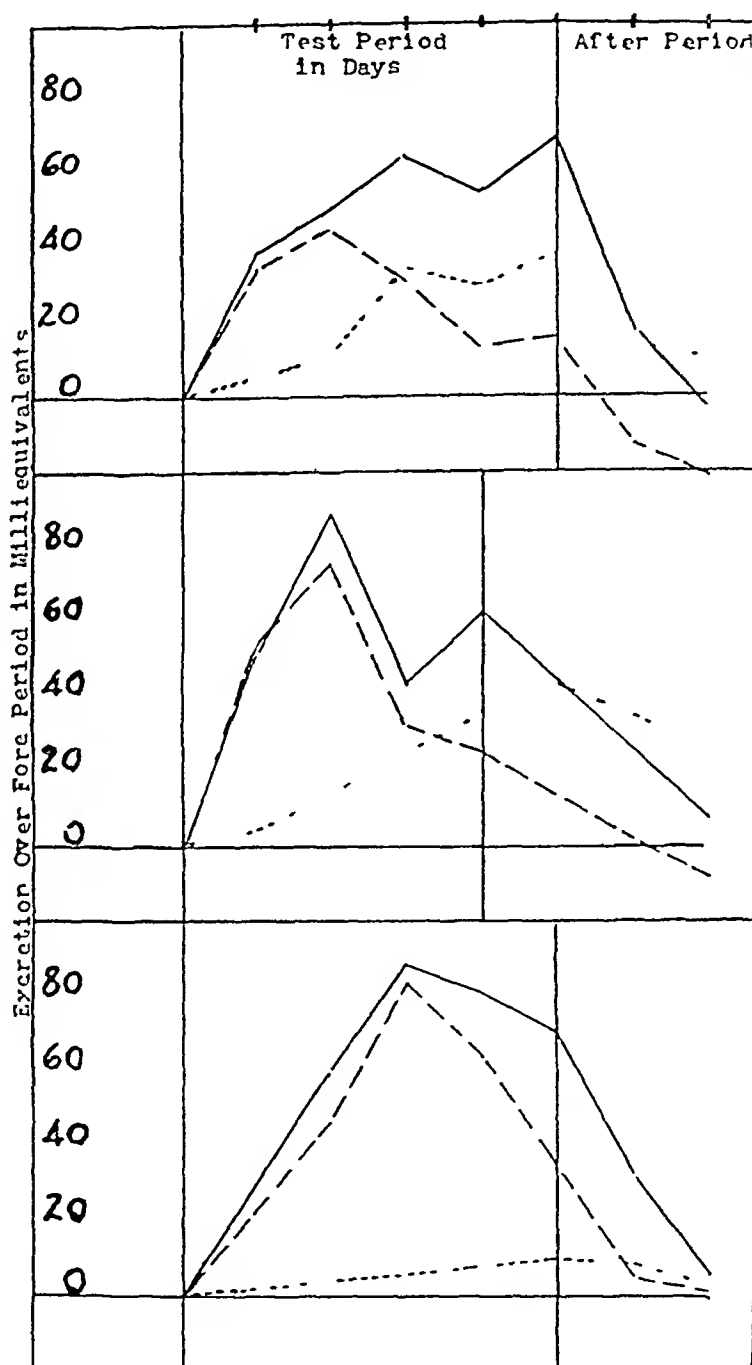
Certain observations of Gamble and his associates¹⁰ and Linder²⁸ should be considered at this point. They have shown that administration of mineral acid leads to the excretion of more extra fixed base in the urine of a subject with impaired kidney function than in that of normal controls. The results of these studies have led to the conclusion that a specific defect in the process of conservation of fixed base exists in the nephritic kidney, and that this defect is intimately connected with the process of ammonia formation, which is proportionately depressed.

In order to study this question further, a number of metabolism experiments similar to those cited have been conducted, and the results

27 A demonstrable lowering of serum chloride could hardly be expected, since diuresis leads to waste of less chloride than of fixed base and the depression of the level of fixed base is very slight.

28 Linder, Geoffrey C. The Effect of Mineral Acid on Acid-Base Regulation in Health and in Nephritis, *Quart J Med* 20 285 (April) 1927.

of three of them, in which cooperation of the subject was satisfactory in regard to collection of urine and adherence to diet, are shown in tables 4, 5 and 6. The results of these studies on nephritic patients without edema are compared graphically in the chart with those on a



Increased excretion of acids and bases in urine on administration of ammonium sulphate. The upper part of the chart represents the results in a subject with normal renal function (case 67075, table 2), the middle part, those in a case of nephritis with edema (A T, table 3), and the lower part, those in a case of advanced nephritis without edema (case 68497, table 6). The excretion of mineral acid is indicated by a solid line, that of fixed base by a long dash and that of ammonia by a short dash.

normal control (table 2) and on the nephritic patient with edema studied by Gamble and his associates¹⁰ (table 3)

It will be observed that in nephritis without edema there is no more waste of base during the first two days of the study than in the normal control and a trifle less than in nephritis with edema. During the last part of the acid test period the waste of base in case 68497, in which

TABLE 2—Case 67075 Normal Renal Function Influence of Ammonium Sulphate on Excretion of Acids and Bases in Urine

Day	(NH ₄) ₂ SO ₄ In gested, M Eq	Urine Vol, cc	Creatinine, Gm	pH	SO ₄ , M Eq	Cl, M Eq	PO ₄ , M Eq	Mineral Acid, M Eq	Na, M Eq	Fixed Base, M Eq	NH ₄ , M Eq	Increase Over Fore Period		
												Mineral Acid	Fixed Base	NH ₄
1	0	960	0.81	5.8	42.4	34.1	32.0	108.5	42.6	88.3	18.4			
2	0	1050	0.88	5.8	47.3	35.3	29.2	111.8	51.7	92.6	20.2			
3	0	1120	0.92	5.6	48.7	37.1	34.4	120.2	47.6	95.1	21.7			
4	75	1080	0.81	5.4	85.5	35.3	32.6	153.2	62.3	127.5	26.2	39.7	35.5	6.1
5	75	1160	0.89	5.0	94.5	40.5	30.1	165.1	78.7	132.4	31.5	51.6	43.4	11.4
6	75	1320	0.90	5.0	100.2	42.8	35.2	178.2	58.2	120.0	54.5	64.7	28.0	34.4
7	75	1010	0.82	5.2	98.6	40.6	29.8	169.0	49.7	105.3	50.6	55.5	13.3	30.5
8	75	1230	0.86	5.2	106.2	41.3	34.4	181.9	51.6	105.0	59.5	68.4	16.0	39.4
9	0	980	0.81	5.4	61.3	40.5	28.5	130.3		79.2	39.4	16.8	-12.8	17.3
10	0	920	0.83	5.6	49.5	31.6	29.0	110.1		71.4	31.5	-3.4	-20.6	11.4

TABLE 3—Case A T Nephritis with Edema* Influence of Ammonium Sulphate on Excretion of Acids and Bases in Urine

Day	(NH ₄) ₂ SO ₄ In gested, M Eq	Urine Vol, cc	Creatinine, Gm	pH	SO ₄ , M Eq	Cl, M Eq	PO ₄ , M Eq	Mineral Acid, M Eq	Fixed Base, M Eq	NH ₄ , M Eq	Increase Over Fore Period		
											Mineral Acid	Fixed Base	NH ₄
1, 2, 3		1070	0.52	4.4	20.4	37.0	32.0	89.4	52.1	18.7			
4	109.0	1200	0.56	4.4	63.6	48.9	33.1	145.6	110.4	23.2	56.2	58.3	4.5
5	109.0	1280	0.57	4.4	89.2	52.0	35.8	177.0	127.7	35.8	87.6	75.6	17.1
6	109.0	1025	0.52	4.8	70.5	30.6	31.9	183.0	81.4	43.3	43.6	29.5	24.6
7	54.5	1030	0.55	4.8	84.3	30.6	36.4	151.3	77.2	56.5	61.9	25.1	37.8
8		1115	0.55	5.0	60.2	40.3	33.8	134.3	66.2	50.1	44.9	14.1	40.4
9		lost											
10		900	0.38	5.2	19.9	45.7	31.9	97.5	43.8	45.8	8.1	-8.3	27.1
11		960	0.52	5.2	17.1	40.0	29.0	86.1	37.2	38.2	-3.3	-14.9	19.5

* Reported by Gamble et al (footnote 10, p. 379)

there was advanced impairment, was somewhat greater than in the case of either the normal control or the nephritic patient with edema.

In attempting to account for the differences observed between normal subjects and patients with different types of nephritis in regard to the quantitative relations of mineral acid and fixed base excreted, it is necessary, aside from renal factors, to consider the changes that take place in the tissues. It seems that a change in the direction of acidosis decreases the capacity of the tissues to bind base and also water, that there is a store of extracellular base, chiefly sodium, which is readily

parted with, and that intracellular base, chiefly potassium, is drained by more severe or prolonged acidosis²⁹ In conditions of edema the tissues tend to become loaded with increased quantities of sodium Consequently, as Gamble and his associates¹⁰ pointed out, the patient with edema would be expected to throw off abnormally large quantities of fixed base with the administration of acid In the ordinary types of chronic glomerular or arteriosclerotic nephritis in adults there is usually

TABLE 4—Case 67985 *Slightly Impaired Renal Function, with No Edema Influence of Ammonium Sulphate on Excretion of Acids and Bases in Urine*

Day	(NH ₄) ₂ SO ₄ In-gested, M Eq	Urine Vol, lme, Ce	Creatinine, Gm	pH	SO ₄ , M Eq	Cl, M Eq	PO ₄ , M Eq	Mineral Acid, M Eq	Na, M Eq	Fixed Base, M Eq	NH ₄ , M Eq	Increase Over Fore Period		
												Mineral Acid	Fixed Base	NH ₄
1	0	980	1.20	5.3	48.7	31.5	29.9	110.1	49.2	100.0	16.8			
2	0	1140	1.32	5.3	53.2	24.4	30.4	108.0	54.0	107.2	22.1			
3	0	1260	1.35	5.4	41.0	38.0	30.2	109.2	52.7	103.2	17.6			
4	96	1450	1.20	5.0	63.8	44.5	38.2	146.5	69.0	134.1	22.8	37.3	30.6	4.0
5	96	1430	1.39	4.8	87.4	41.3	33.9	172.6	61.5	138.7	30.9	63.4	35.2	12.1
6	96	1560	1.32	4.4	85.3	53.0	38.0	176.3	54.0	133.0	38.4	67.1	29.5	19.6
7	96	1710	1.40	4.4	91.6	61.4	38.1	191.1	57.2	142.9	47.3	115.3	39.4	28.5
8	96	1740	1.35	4.4	89.0	50.6	37.4	177.0	56.0	141.0	42.8	81.9	37.5	24.0
9	0	1610	1.32	4.6	72.8	51.3	29.5	153.6	49.6	110.2	45.6	44.4	6.7	26.8
10	0	1220	1.15	4.9	37.3	28.9	32.2	98.4	41.0	86.0	27.5	-10.8	-17.2	8.7

TABLE 5—Case 67156 *Advanced Renal Impairment, with No Edema Influence of Phosphoric Acid on Excretion of Acids and Bases in Urine*

Day	H ₃ PO ₄ In-gested, M Eq	Urine Vol, lme, Ce	Creatinine, Gm	pH	SO ₄ , M Eq	Cl, M Eq	PO ₄ , M Eq	Mineral Acid, M Eq	Na, M Eq	Fixed Base, M Eq	NH ₄ , M Eq	Increase Over Fore Period		
												Mineral Acid	Fixed Base	NH ₄
1	0	1720	1.23	5.8	31.2	78.5	29.4	139.1	66.7	139.5	8.8			
2	0	1770	1.28	5.8	28.0	86.0	29.6	143.6	67.3	138.2	7.1			
3	110	2150	1.37	5.8	30.7	93.5	55.3	179.5	76.1	166.0	13.4	38.1	27.2	5.4
4	110	2180	1.26	5.0	33.2	106.1	70.0	209.3	74.1	190.9	20.5	67.9	52.1	12.5
5	75	1700	1.05	4.6	37.5	98.0	67.6	203.1	65.7	174.4	18.5	61.7	35.6	10.5
6	0	1890	1.15	5.0	38.7	96.8	43.5	179.0	48.0	155.5	19.3	37.6	16.7	11.3
7	0	1600	1.12	5.0	34.8	85.3	35.8	160.1	50.6	132.8	17.1	18.7	4.0	5.1

no edema except with heart failure or some other complication, and on account of the acidosis that accompanies the renal impairment the supply of easily mobilized fixed base of extracellular fluid should be somewhat depleted Separate analyses do show low figures for extra sodium excretion in the nephritic patient (tables 4 and 5) as compared with the normal subject (table 2) This fact may account in part for the relatively small quantity of extra fixed base excreted in the urine

²⁹ Haldane, J. B. S., Hill, R., and Luck, J. M. Calcium Chloride Acidosis, *J. Physiol.* **57**: 301 (June) 1923. Gamble et al. (footnote 10)

during the first days of acid administration³⁰ However, a much more severe grade of acidosis develops in the patient with renal impairment than in the normal control on a given dosage of mineral acid, so after prolonged administration more intracellular fixed base is released from the tissues of the nephritic patient

In looking for renal factors to account for excretion of abnormally large quantities of fixed base with ingestion of acid, attention is again directed to the question of a diuresis that seems to handicap in some way the mechanism for conservation of base The tables show that there was a definite and prolonged increase in the volume of urine in nephritic patients on ingestion of acid A diuresis of the magnitude observed would probably not be great enough appreciably to handicap

TABLE 6—Case 68497 Advanced Renal Impairment, with No Edema Influence of Ammonium Sulphate on Excretion of Acids and Bases in Urine

Day	(NH ₄) ₂ SO ₄ Ingested, M Eq	Urine Vol ume, Cc	Creat- inine, Gm	p _H	SO ₄ , M Eq	Cl, M Eq	PO ₄ , M Eq	Min eral Acid, M Eq	Fixed Base, M Eq	NH ₄ , M Eq	Increase Over Fore Period		
											Min eral Acid	Fixed Base	NH ₄
1	0	2560	1.08	5.0	41.5	130.0	31.8	208.3	174.7	8.1			
2	0	2940	1.22	4.9	46.2	124.4	41.2	211.8	210.9	8.6			
3	0	2950	1.23	5.0	45.7	138.4	40.0	224.1	220.2	9.3			
4	96	2540?	0.90	4.9	44.7	120.6	29.6	194.9	175.4	8.9	?	?	?
5	96	3100	1.15	4.8	81.6	144.1	36.4	262.1	247.2	12.4	49.0	45.2	4.1
6	96	3310	1.29	4.8	102.5	157.2	40.8	300.5	305.7	13.9	87.4	83.7	5.3
7	96	3320	1.30	4.9	107.4	143.9	42.8	294.1	265.8	16.5	81.0	63.8	7.9
8	96	3390	1.31	4.9	101.2	142.8	40.8	284.8	239.0	19.2	71.7	37.0	10.6
9	0	2950	1.19	4.9	82.3	124.5	38.9	245.7	207.5	18.3	32.6	5.5	9.7
10	0	2980	1.14	4.9	63.8	126.1	37.8	227.7	205.0	12.5	14.6	3.0	3.9

the base-conserving mechanism in health, but superimposed on the prevailing compensatory diuresis in a kidney remnant, it might be expected tremendously to increase the rate of flow through the tubules and so lead to excretion of much extra fixed base In addition to the pronounced increase in the excretion of fixed base, there is a conspicuous increase in excretion of chloride and a lesser increase in excretion of phosphate, results that are also consistent with a diuretic effect In the experiment of Gamble (table 3) the drop in the excretion of fixed base was associated with a drop in the volume of urine

An additional experiment has been conducted to bring out the changes in excretion of inorganic acids and bases with fluctuations in the volume of the urine caused by decreasing and increasing the intake of distilled

30 In one case of nephritis without edema studied by Linder (footnote 28) a surprisingly large quantity of potassium was excreted at the onset of acid administration Some quantitative error was indicated, however, since the p_H values show that the urine was more acid, while extra fixed base excretion considerably exceeded the extra mineral acid excretion

water. The results in table 7 show, with a diuresis of the order produced in the previous experiments, an increase in excretion of inorganic acids and a considerably greater increase in the excretion of fixed base. The changes in fixed base are not so great as those obtained by the administration of acid, presumably because the acid effect in the tissues is lacking.

The conclusion to be drawn is that changes in the excretion of fixed base caused by the administration of acid may be accounted for by a movement of fixed base from the tissues to the blood stream and to the urine and by a diuretic effect that handicaps reabsorption.

THE RÔLE OF THE AMMONIA SECRETED IN THE URINE

Since ammonia formation in nephritis is depressed along with functional impairment, considerable interest has necessarily centered on the relation of this activity to the inorganic disturbance. The strong impres-

TABLE 7—Case 68497 *Advanced Renal Impairment Influence of Distilled Water Diuresis on Excretion of Acids and Bases in Urine*

Day	Water Ingested, Cc	Urine Volume, Cc	Creatinine, Gm	SO ₄ , M Eq	Cl, M Eq	PO ₄ , M Eq	Mineral Acid, M Eq	Fixed Base, M Eq	NH ₄ , M Eq	Increase Over Fore Period		
										Mineral Acid	Fixed Base	NH ₄
1	2500	2620	1.20	38	102	41	181	152	18			
2	1500	2040	1.20	35	77	38	150	118	21	-31	-34	+3
3	4000	3680	1.32	42	107	48	197	188	22	+16	+31	+4

sion gained during the course of this study is that the formation of ammonia serves chiefly to prevent excess acidity of the genito-urinary tract.

It has been observed in the first place that there is no serious depletion of serum fixed base even with advanced functional impairment, and the threshold values obtained may very well be due to a sustained compensatory diuresis. Then it was pointed out that the influence of acid on fixed base excretion in either normal conditions or different types of nephritis could be accounted for by a consideration of the effect of the acid on the base and water binding capacity of the tissues and the effect of the diuresis on reabsorption of fixed base.

The conventional teaching³¹ that the formation of ammonia serves as an important factor in neutrality regulation in the body seems an unavoidable conclusion only as long as one supposes the ammonia to be formed in the tissues and neutralized by metabolic acids before reaching the kidney. The widely accepted view at present, however, is that the ammonia is formed by the kidneys,³² although this was vigorously

31 Henderson, Lawrence J. A Critical Study of the Process of Acid Excretion, *J Biol Chem* 9 403, 1911.

32 Benedict, Stanley R, and Nash, Thomas P. On the Question of the Origin of Urinary Ammonia *J Biol Chem* 82 673 (June) 1929.

opposed by Bliss³³ The view that ammonia is formed to prevent excess acidity carries the implication that a primary secretion of high acidity is formed, since the bladder urine is slightly acid even after the formation of much ammonia The interesting observations of Macallum and Campbell³⁴ indicate that a primary secretion of high acidity is formed In this study of Macallum it was observed after intravenous administration of a solution of ferric ammonium citrate and sodium ferrocyanide to fasting experimental animals that prussian blue was formed in the cells of the proximal convoluted tubules and carried down into the urine Prussian blue is not formed when the solution is added to a saturated solution of potassium dihydrogen phosphate, as was pointed out by Macallum When it is added to tenth-molar lactic acid, a greenish coloration is formed, and in the presence of stronger acid the intense coloration of prussian blue is observed

If, as Macallum believes, the primary renal secretion has an acidity comparable with that of gastric juice, it follows that the essential of fixed base conservation, i e., formation of a secretion containing a large excess of acid over fixed base, is effected in the proximal convoluted tubules, that the ammonia is added later, or the primary secretion would not have been more acid than the bladder urine, and that the primary secretion, if not neutralized by ammonia or some other base, would be extremely irritating to the genito-urinary tract It is obvious that whether the conventional view or the one suggested here is correct, ammonia and fixed base are complementary factors in neutralizing the acid of the urine, and with administration of alkali ammonia formation is depressed In the curves showing the results of the administration of acid one observes about the same activity in the formation of ammonia on the second day of acid administration, a period of base waste, as on the second day of the after-period, a period of base conservation In both cases the quantity of ammonia formed is just about sufficient to neutralize the excess of mineral acid over fixed base In certain other cases the quantity of ammonia formed is not determined by waste or conservation of base but by the excess of acid over fixed base that is being excreted One of these conditions is in the diuresis produced by drinking distilled water, increased quantities of fixed base are lost by the tissues into the urine, but the formation of ammonia is not stimulated Another case is found in the study of Fiske and

33 Bliss, Sidney The Amide Nitrogen of Blood III Muscular Exercise The Role of Ammonia in the Neutralization of Lactic Acid, *J Biol Chem* **81** 137 (Jan) 1929

34 Macallum, A B and Campbell, W R The Secretion of "Acid" by the Kidney, *Am J Physiol* **59** 439 (Oct) 1929

Sokhey³⁵ They observed that when mineral acid was injected intravenously at a very slow rate, considerable extra fixed base was excreted and some extra ammonia formed, but when the acid was injected slightly faster, the respiratory center was so violently stimulated that alkalosis developed, more fixed base than before was lost from the tissues, and yet ammonia formation was depressed

RELATION OF CERTAIN CLINICAL CONSIDERATIONS TO THE INORGANIC DISTURBANCE

Polyuria—The secretion of large volumes of urine in chronic nephritis with retention of waste products has already been accounted for on the basis of a sustained compensatory diuresis in the kidney remnant. In order to obtain a clearer picture it may be supposed that, whereas in health about 150 liters of glomerular fluid are formed in a day and 1 per cent escapes reabsorption, leaving a volume of urine of 1.5 liters, with moderately advanced impairment only 50 liters of glomerular fluid are formed and 4 per cent escapes reabsorption, owing to the increased rate of flow, leaving 2 liters of urine.

Acidity of the Urine—The urine tends to be more acid than normal with advanced renal impairment³⁶. Compared with a normal subject on the same diet, a nephritic patient excretes similar quantities of the various acid waste products because of higher equilibrium levels in the blood stream. The level of fixed base in serum, and presumably that of glomerular fluid, is maintained at a slightly lower level with renal impairment, but the reabsorption of fixed base is not quite so perfect. The result is that the nephritic patient excretes about the same quantity of fixed base as the normal control on the same diet (Gamble et al.¹⁰). The greater acidity of the urine in nephritis depends, therefore, on the formation of less ammonia. The interpretation offered here is that the primary secretion of high acidity is not so completely neutralized by the formation of ammonia, because it is forced at a relatively high speed through relatively few tubules.

Edema—There are two factors operating in nephritis with destruction of glomerular tissue that tend to prevent rather than to cause edema. The first is the poor tubular reabsorption and polyuria resulting

35 Fiske, Cyrus H., and Sokhey, S. S. Ammonia and Fixed Base Excretion After the Administration of Acid by Various Paths. *J. Biol. Chem.* **63** 309 (March) 1925.

36 Henderson, Lawrence J., and Palmer, W. W. On the Intensity of Urinary Acidity in Normal and Pathological Conditions, *J. Biol. Chem.* **13** 393, 1912-1913.
McCorvie, John E. Studies on the Morning Alkaline Tide of Urine in Normal Persons and in Patients with Nephritis. *J. Clin. Investigation* **2** 35 (Oct.) 1925.
Magnus-Levy, A. Das Ammoniak bei der Nephrose, *Ztschr. f. klin. Med.* **112** 256 1930.

apparently from an increased rate of flow. The other factor is the acidosis, which decreases the power of the tissues to bind water. Edema, when occurring in the arteriosclerotic types of nephritis, is nearly always due to heart failure, and the impression in this clinic is that patients with cardiac disease and renal impairment have less trouble with pulmonary and subcutaneous edema than those with good renal function. If there is any renal factor, aside from that which permits albuminuria, tending to cause edema, it should be looked for in the activity of the tubules as well as in that of the glomeruli, since the tubules are thought to be especially concerned with return of water and fixed base to the tissues. It is interesting to observe in this connection that the types of kidney disease associated with edema are those in which cells of the renal tubules show edema and various degenerative changes with little atrophy or necrosis, i. e., changes that might be looked on as irritation phenomena. If these changes are compatible with excessive functional activity,³⁷ then excessive quantities of water and fixed base would be returned to the tissues and would tend to cause scanty urine and edema. The levels of creatinine and other waste products in the blood stream and the quantities excreted in the urine are usually normal in the degenerative types of nephritis, in which edema is most troublesome. Calculations by the method of Rehberg,²⁴ therefore, indicate the formation of a normal quantity of glomerular fluid with scanty urine. The conclusion, then, seems forced that excessive reabsorption of water does occur as a cause of edema in degenerative nephritis.

Uremia—The group of symptoms associated with the uremic syndrome are those to be expected from asphyxia, particularly asphyxia of various centers in the brain. In acute hemorrhagic nephritis, uremic manifestations are controlled by agents that relieve the edema of the brain (Blackfan³⁸). When nephrosis terminates fatally, coma or other signs of uremia may be attributed to edema of the brain. In the arteriosclerotic type of nephritis, circulatory disturbances in the brain due to blood vessel changes or cardiac stasis are probably the most important factors in causing any manifestations of uremia that may be present.

The question of special interest here is whether or not the acidosis may be a contributing cause in the production of uremia. Koehler³⁹ found that administration of more than 15 Gm of phosphoric acid or

37 Magnus-Levy (footnote 36, third reference) observed increased capacity of the kidney in nephrosis to produce ammonia and attributed this to an irritated state of the tubular epithelium.

38 Blackfan, Kenneth D. Acute Nephritis in Children, with Special Reference to the Treatment of Uremia, *Bull. Johns Hopkins Hosp.* **39** 69, 1926.

39 Koehler, Alfred E. The Effect of Acid and Base Ingestion upon the Acid-Base Balance. *J. Biol. Chem.* **72** 99 (March) 1927.

large doses of ammonium chloride or calcium chloride daily for a week or more to persons with normal kidney function gradually produced a marked fall in plasma carbon dioxide and p_{H} . With this severe prolonged acidosis he observed the following symptoms: headache, loss of appetite, nausea, drowsiness and muscle pains. These are the same symptoms found by Feinblatt⁴⁰ to be especially characteristic of uremia. Koehler pointed out that the symptoms are probably the result of tissue asphyxia, since tissue oxidation is at its optimum at a normal p_{H} . It would seem then that, although the chief causes of the symptoms of uremia that appear in the various types of nephritis are due to edema or circulatory disturbances in the brain, the presence of severe acidosis due to retention of phosphoric and sulphuric acids might increase the tendency toward asphyxia and be a contributory factor in producing the syndrome. In types in which edema of the brain is present, however, the analysis is complicated by the fact that the acidosis tends to reduce the edema. Acidosis up to a certain extent could then be beneficial when a greater degree would be detrimental.

That there is a decreased tolerance to mineral acids in chronic nephritis with impaired renal function is certain. This fact was observed by Gamble and his associates¹⁰ and Linde²⁸ for sulphuric and hydrochloric acids. In the present study a number of patients with arteriosclerosis and impaired renal function showed poor tolerance to phosphoric acid or ammonium sulphate. In case 64392 the administration of phosphoric acid, 6 Gm daily, was begun on Feb 2 1929, and on February 4, headache and nausea developed, symptoms that disappeared promptly when the phosphoric acid was discontinued. The patient in case 64838, with more advanced renal impairment, started to take phosphoric acid, 6 Gm daily, on March 5, 1929 and generalized muscle pains and loss of appetite developed the following afternoon. The patient in case 67156, who had arteriosclerosis and advanced renal impairment and was given the same dosage of phosphoric acid, on the third day complained of general malaise, muscle tremors and nausea. The patient in case 67024, with advanced arteriosclerosis and renal impairment, took ammonium sulphate equivalent to 96 cc of normal sulphuric acid, starting on March 13, 1930. He was observed to be quite drowsy and to vomit his evening meal on March 16. The patient in case 68497, with advanced renal impairment but not such extensive arteriosclerosis, was able, during the metabolism test starting Oct 8, 1930, to take ammonium sulphate equivalent to 96 cc of normal acid daily for five days without developing any symptoms of uremia, although blood taken on the last day showed a lower level

⁴⁰ Feinblatt, H. M. Uremia, the Syndrome of Nitrogen Retention, Boston M. & S. J. **189** 399 (Sept 20) 1923.

of p_H than was observed with the onset of uremic symptoms in cases 67024 and 67392. The suggestion is that in the last patient, who had less advanced cerebral arteriosclerosis, there was less tendency to cerebral asphyxia. Other patients with rather advanced arteriosclerosis and only slight impairment of renal function have been able to tolerate considerably greater quantities of ammonium sulphate or phosphoric acid.

Treatment—The problem in treatment for the acidosis in nephritis is to replace fixed base depletion and to promote excretion of, or limit accumulation of, sulphuric and phosphoric acids. The results of this study tend to minimize considerably the necessity for replacement of fixed base, since in uncomplicated cases the level of fixed base is scarcely below the limits of normal fluctuation.

The influence of alkali on the retention of acid in nephritis has been chiefly concerned with phosphoric acid. Marriott and Howland,⁴¹ in an early study, found no evidence that administration of sodium alkali promoted excretion of phosphate in nephritis. In a previous study,⁴² I observed that the administration of potassium or magnesium acetate failed to influence the excretion of phosphate in the urine. Administration of calcium salts, however, has been shown to decrease the excretion of phosphate in the urine⁴³ and to increase excretion in the feces, presumably because unabsorbed calcium tends to bind phosphoric acid split off during digestion, and calcium that is absorbed is excreted in the feces for the most part and carries phosphate along in combination. It will be observed that the patients in cases 62367 and 64838, who took calcium carbonate, 6 Gm daily, did show a definite drop in the level of serum phosphate. Marriott and Hartmann⁴⁴ also spoke of reducing the level of serum phosphate in nephritis by calcium therapy.

Along this same line some attention has been given to the question of strontium therapy. Strontium, like calcium, is excreted chiefly in the feces and has an insoluble sulphate as well as a phosphate. It is conceivable, then, that strontium therapy in chronic nephritis might facilitate the removal through the intestine of sulphuric as well as phosphoric acid. Intraperitoneal administration of strontium acetate

41 Marriott, W. McKim, and Howland, J. Phosphate Retention in Nephritis, *Arch Int Med* **18** 708 (Nov.) 1916.

42 Briggs, A. P. Some Metabolic Aspects of Calcium Therapy, *Arch Int Med* **37** 440 (March) 1926.

43 Telfer, S. V. Studies in Calcium and Phosphorus Metabolism. III. The Absorption of Calcium and Phosphorus and Their Fixation in the Skeleton, *Quart J Med* **17** 245, 1924. Briggs (footnote 42).

44 Marriott, W. McKim, and Hartmann, Alexis F. Newer Aspects of Acidosis, *J. A. M. A.* **91** 1675 (Dec. 1) 1928.

in dogs caused a conspicuous drop in the urinary excretion of phosphate and a very slight drop in sulphate, suggesting that strontium phosphate and sulphate had been excreted in the feces⁴⁵ In the present study, a drop in the levels of both serum phosphate and sulphate after administration of strontium carbonate, 6 Gm daily, was observed in the following instances in case 64123, on Dec 29, 1928, in case 66998, on April 21, 1930, in case 67392, on April 25, 1930, and in case 68497, on Dec 20, 1930 With the drop in sulphate and phosphate there is a slight rise in bicarbonate and p_H , that is, a partial correction of the acidosis

Having partially corrected the acidosis, it would be gratifying to be able to report associated clinical improvement As pointed out, however, this work has been done on patients without symptoms Moreover, the early appearance of nausea as a symptom has so far interfered with the use of strontium therapy in uremia It will be interesting to see, however, if the continuous administration of calcium or, better, of strontium carbonate to a nephritic patient will prolong the course before the appearance of symptoms

In attempting to evaluate the efficacy of the high base diets introduced by Sansum, Blatherwick and Smith⁴⁶ for treatment in nephritis, a number of points should be observed Evidence was just presented that the sodium and potassium alkalis of such diets do not promote excretion of phosphoric acid, and in addition it might be mentioned that Shohl and Sato⁴⁷ found that administration of sodium bicarbonate failed to influence appreciably the excretion of any acid Moreover, a diet consisting chiefly of fruits and vegetables has been found to provide insufficient protein in cases in which albuminuria is severe⁴⁸ When protein (high phosphorus and sulphur) foods are incorporated in the diet, nothing seems to be accomplished in the way of eliminating the resulting acids by ingestion of a quantity of fruit and vegetables (sodium and potassium alkali) A special case is observed when milk is used to provide the necessary protein In this instance the high phosphorus content of the milk is balanced by a high calcium content, which seems to facilitate the elimination of phosphorus through extrarenal channels From the foregoing evidence it would seem that the ordinary high base diet has for its chief merit an associated limitation of phosphoric and sulphuric acids

45 Unpublished experiments

46 Sansum, W D, Blatherwick, N R, and Smith, Florence H The Use of Basic Diets in the Treatment of Nephritis, *J A M A* **81** 883 (Sept 15) 1923

47 Shohl, A T, and Sato, A Acid-Base Metabolism II Mineral Metabolism, *J Biol Chem* **58** 257 (Nov) 1923

48 Peters, John P, and Bulger, Harold A The Relation of Albuminuria to Protein Requirement in Nephritis, *Arch Int Med* **87** 153 (Feb) 1926

SUMMARY AND CONCLUSIONS

The acid-base equilibrium has been studied in a group of nephritic patients in whom vomiting and other complications were negligible

It has been observed that the condition of the serum acids is very similar to that found after ligation of both ureters in experimental animals. There is, however, a very slight depression in the level of serum fixed base. It has been observed that prolonged administration of mineral acid to these nephritic patients (without edema) leads to waste of more base than in normal controls.

It has been concluded that the defect in conservation of base, as well as of water, chloride and other substances, depends largely on an increased rate of flow of the glomerular fluid through the surviving tubules.

It has been concluded that the chief function served by ammonia formation is the prevention of excess acidity in the genito-urinary tract.

An attempt has been made to apply the experimental findings and theoretical considerations to various clinical and therapeutic features of nephritis.

TUBERCULOSIS AMONG NURSES

EVERETT K GEER, M D

ST PAUL

The subject of this paper is not new, but it has not been given adequate attention, and because of its importance merits extensive study Heimbeck¹ in Norway, Ross² in Canada, Shipman and Davis,³ and Whitney⁴ in this country have sensed the problem and have suggested corrective measures that are satisfactory only in part, because none of these writers has sought to prevent contagion, which in my experience is the essence of the question Furthermore, as this inquiry progressed it appeared to me that this might be a study that would throw more light on the pathogenesis of tuberculosis

The present investigation was undertaken because there seemed to be an unusually high incidence of tuberculosis among student nurses at the Ancker Hospital in St Paul This institution is the city and county hospital for St Paul and Ramsey County It has 975 beds, 215 of which are devoted to patients with tuberculosis and form the Ramsey county sanatorium The nurses for the tuberculosis pavilion come from the nurses training school of the hospital and in the main are from rural communities Their average age on entering training is from 18 to 20 years The nurses devote approximately four months of the three years of training to the care of patients with tuberculosis and part of this training is given the first year

On looking over the records in the training school office, it was found that 42 nurses from a total of 934, or 4.5 per cent, had broken down with tuberculous disease from 1920 to 1928, either during training or shortly afterward For many years, all nurses entering training have been given physical examinations, and beginning in 1926, roentgenograms of the chest have been taken Preventive inoculations against

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† Read before the staff of Lymanhurst School Minneapolis, on Sept 23, 1930, the Mississippi Valley Sanatorium Association, at Rockford, Ill., on October 14, the Minnesota Society of Internal Medicine at Rochester, Minn., on November 10 and the Minnesota Pathological Society on Jan 20, 1931

1 Heimbeck, Johannes Immunity to Tuberculosis, Arch Int Med **41** 336 (March) 1928

2 Ross, E L Canad M A J **22** 347, 1930

3 Shipman, S J, and Davis, E A Am J Nursing **23** 8, 1928

4 Whitney, J S Am J Nursing **23** 8, 1928

smallpox and diphtheria are also given, weights are recorded periodically, and physical examination repeated when it is considered necessary.

It was thought that routine skin tuberculin tests might throw some light on the problem of tuberculosis, so in September, 1928, I began to test the incoming class of probationers. All the tests have been given intradermally, and, with the exception of the first two groups, I have used tuberculin made from the H 37 strain of tubercle bacillus sent to me by Dr. Allen K. Krause. One-tenth milligram has been given at the first injection, and if the reaction has been negative the test has been repeated in forty-eight hours with a dosage of 1 mg. The scale for reading the reactions has been essentially that used by Opie and McPhedran.

Of the 32 young women entering training in September, 1928, 10 gave positive and 22 negative reactions. This result was not surprising, as it was comparable to the findings of Lees and Myers⁵ in testing freshmen at the University of Minnesota, a similar age group from practically the same community.

I was curious to know what reaction the remainder of the training school students would show, and was amazed to discover that of 147 nurses, 143 gave positive reactions and only 4 negative. In other words, nearly all of the nurses who had been in training for six months or more were infected, in contrast to an entering group only one third of whom were infected.

These findings provided food for thought. Was it true that in Minnesota only from 30 to 35 per cent of the young people reaching the twenties had acquired tuberculous infection? Slater's⁶ work tends to prove this, and Lees and Myers'⁵ observations substantiate it, as do those of Laird, Guyer and Bailey,⁷ although as late as 1929, Rich and McCordock⁸ spoke of the late adults "who escape the protective infection of childhood." It is known that tuberculous infection may become so thoroughly overcome that the skin reaction becomes negative. Opie and McPhedran,⁹ Krause,¹⁰ Austrian¹¹ and others have noted this,

5 Lees, H. D., and Myers, J. A. *Am Rev Tuberc* **21** 532, 1930.

6 Slater, S. A. *Am Rev Tuberc* **10** 299, 1924.

7 Laird, A. T., Guyer, L. G., and Bailey, W. *Am Rev Tuberc* **24** 207, 1926.

8 Rich, O. R., and McCordock, H. A. *Bull Johns Hopkins Hosp* **44** 370, 1929.

9 Opie, E. L., and McPhedran, F. M. *Am Rev Tuberc* **24** 362, 1926.

10 Krause, A. K. *Am Rev Tuberc* **11** 303, 1925.

11 Austrian, C. R. *Tubercle* **6** 29, 1924.

although it is uncommon. In my experience in following up the children who have left the Children's Preventorium of Ramsey County since 1915, only 10 of more than 400 who gave positive reactions later gave negative reactions. A percentage such as this would not materially affect the results noted in the incoming nurses. In fact, all the evidence points to the conclusions that the incidence of tuberculous infection in young adults of Minnesota is low.

My next thought was whether or not this low incidence of tuberculous infection should influence the selection of the nursing personnel for our tuberculosis institutions. I think it advisable in all sanatoriums and hospitals to give all nurses on entering training physical and roentgen examinations and to make skin tests. An important question is whether or not nonreacting nurses should be permitted to care for consumptive patients. Should such nurses be kept out of sanatoriums and away from tuberculosis departments of general hospitals? The old dictum that sanatoriums are the safest places to be in so far as tuberculosis is concerned finds little support in this investigation. Heimbeck's¹ use of BCG for his nonreacting nurses is hardly warranted as yet, furthermore, it is the wrong approach. Institutions can and should be made safe from the standpoint of contagion, and then there will be less cause to worry about nurses or other employees. In the light of present knowledge concerning the immunology of tuberculosis and in view of the inadequate medical aseptic measures now used in most tuberculosis institutions, I am convinced that nonreacting nurses who come in contact with tuberculous patients are in a more precarious situation than the reacting nurses, because a large majority of the former have not had the protective infection of childhood. Some doubtlessly will argue that nonreacting nurses should be kept away from tuberculosis institutions, and others will contend that nurses who exhibit a highly allergic state should also be excluded from nursing tuberculous patients. These apparent paradoxical points of view will have little support if precautions are taken to protect nurses from frequent and massive doses of tubercle bacilli. There must be nurses, so it is necessary to make their working environment safe. This implies not only careful general supervision of working hours, adequate food and opportunities for rest and recreation, but connotes rigid contagious technic when the nurses are on duty with tuberculous patients.

Since September, 1928, I have been testing all incoming nurses at the Ancker Hospital and retesting, every six months, those who gave a negative reaction. An interesting observation has been that those originally showing a negative reaction have had, without exception, 3

or 4 plus reactions when they have become positive, which must be interpreted as showing recent infection. The results of this periodic retesting is shown in the accompanying chart.

It seemed worth while to test nurses in other hospitals in St. Paul to see what the incidence of tuberculous infection was in institutions without tuberculosis departments. Table 1 shows the results of these tests.

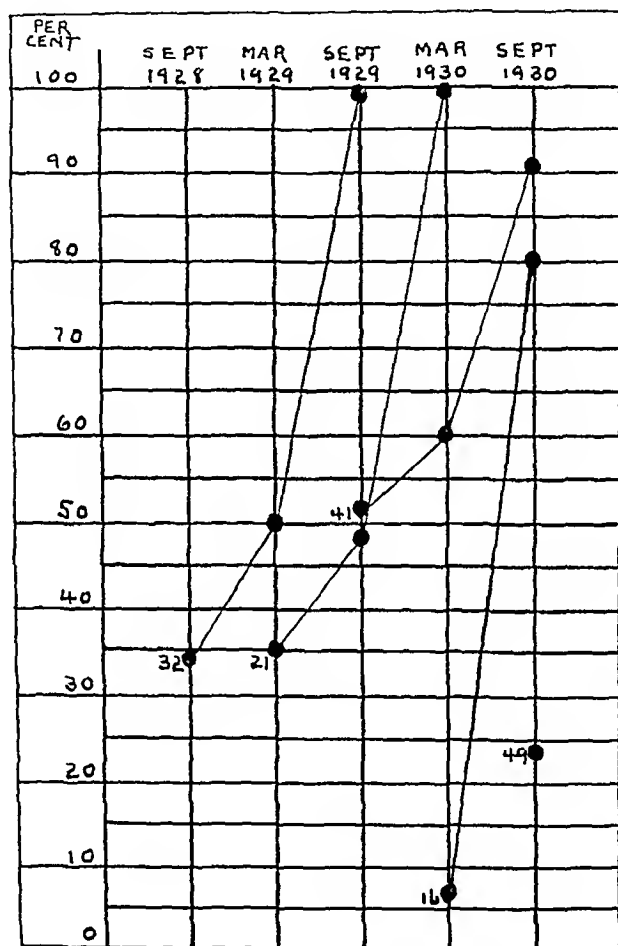


Chart showing the number of women entering training at Ancker Hospital, spring and fall, since September, 1928, the percentage of those who gave positive reactions originally and the rapid increase in this percentage at six-month intervals.

Likewise it appeared advisable to investigate a group similar to the Ancker nurses. The University of Minnesota Hospital Training School offered this opportunity, as its nurses are sent to Glen Lake Sanatorium for a period of from six to eight weeks. The results of the test are shown in table 2.

There is another group of nurses in the Ancker Training School that I have tested concerning which it is difficult to draw conclusions. Since September, 1928 I have tested 114 nurses who have been affiliated

with the Ancker School or transferred from other hospitals. In the main, these nurses have come from small institutions in the Northwest, and the time they have spent in training elsewhere has varied. Of these 114, 81 gave a positive reaction and 33, a negative one, a percentage incidence of those giving positive reactions of 71 plus. It is interesting to compare this group with the group from other St. Paul hospitals.

Since 1928, Dr. F. F. Callahan has been testing nurses at Pokegama Sanatorium. This is a small private institution having a two

TABLE 1—*Showing a Combined Tabulation of Tests of Student Nurses at Bethesda, Midway, Mounds Park, St. John's and St. Luke's Hospitals in St. Paul.*

Year in Training	Number Tested	Positive		Negative	
		Number	Per Cent	Number	Per Cent
First	95	38	40	57	60
Second	70	34	48.6	36	51.4
Third	45	19	42.2	26	57.7
Total	210	91	43.3	119	56.6

* The procedure used at Ancker Hospital of testing nurses on entering training and retesting every six months was impossible in these hospitals. By tabulating according to the year in training, the intention was to ascertain whether or not the incidence of infection increased with the length of time in training.

TABLE 2—*Showing Results of Testing Student Nurses from the University of Minnesota Hospital Training School.*

Glen Lake Service	Number Tested	Positive		Negative	
		Number	Per Cent	Number	Per Cent
Before	291	138	47.4	153	52.6
After	65	55	84.6	10	15.4

* No attempt was made to separate this group into years of training. The purpose was to ascertain the difference, if any, between nurses who had had, and those who had not had, service at Glen Lake Sanatorium.

year training course which draws largely former patients as students. Consequently, the findings in this small group would necessarily vary from those in the Ancker group. In the past two years, 13 young women have entered training at Pokegama. Only 2 of them gave a negative reaction on admission, but the reactions became positive within a year. In one of those with a positive reaction pleurisy with effusion developed while she was in training, and in another a frank parenchymatous lesion developed, the latter nurse had a sister with pulmonary tuberculosis and a year before entering training this nurse had had a definite hemoptysis without other symptoms.

It appears incontrovertible that women entering the nurses' training school at Ancker Hospital have an average incidence of tuberculous infection of about 30 per cent, and that by the end of the three year

training period, and usually within the first year, practically all are infected, which is in agreement with Heimbeck's¹ findings. This is in startling contrast to what happens in other hospitals in St. Paul, then nurses show an incidence of 42 per cent in the last year of training. As all come from a similar age group in the same community, it seems fair to assume that the nurses from the Ancker Hospital acquire infection because part of their training brings them in contact with cases of open pulmonary tuberculosis.

As to the technic used in the tuberculosis pavilion of Ancker Hospital and as to whether or not patients receive instructions, all nurses going to the pavilion are told that they are handling a communicable disease. They are instructed and told repeatedly to wash their hands after giving bedside care and before going to meals. They are told to insist on patients covering the mouth and nose when coughing or sneezing. They are cautioned to keep their hands away from their nose and mouth. They wear gowns and gauze masks. They receive instruction as individuals and in small groups, as well as in formal class lectures. The patients are given monthly talks by radio covering the various phases of tuberculosis, besides innumerable individual and ward talks, and they are also encouraged to read books written for patients.

Despite these measures, the nurses become infected and some of them massively so. One serious obstacle to be overcome is a psychological one. It is readily appreciated how a nurse in the contagious department, caring for a patient with diphtheria or scarlet fever, would be impressed by the acute illness and be meticulous in her personal precautions. It is just as understandable how she might unconsciously become careless in a ward of consumptives, where the appearance of some of the patients is such that the uninformed person wonders why they are kept in bed.

In order partially to overcome this difficulty and because, after all, tuberculosis is a communicable disease, may it not be wise to insist on the most rigid contagious technic in sanatoriums and tuberculosis departments of general hospitals, especially in those communities in which the incidence of tuberculous infection in young adults is low? It would impress nurse and patient alike, and it is my conviction that it should be done.

Another factor of importance, particularly in large municipal hospitals and probably to a less extent in private general hospitals, is the unrecognized, undiagnosed case of consumption. No nurse can protect herself fully against an infectious disease unless she knows what type of patient she is nursing. The number of persons sent into general hospitals for observation is large. Many elderly people are

admitted for a variety of complaints who give a history of an apparently innocuous bronchitis of many years' duration. A goodly number of persons in the teens are sent to hospitals for conditions that appear to be pneumonia, influenza or acute bronchitis, but after one, three or six weeks, it is found that tuberculosis is present. This unseen danger, the patient with an undiagnosed case of consumption, is a very real one to nurses, and I know from experience that it exists in the general wards at Ancker Hospital.

The solution of this difficulty lies to no small degree in first, taking a roentgenogram of the chest of every patient admitted to general hospitals, just as urinalysis, hemoglobin and white cell counts are made so generally, second, instructing nurses to send to the laboratory all sputum that the patients may raise. These two measures should be incorporated into the routine of every hospital, as they would largely eliminate the menace of unrecognized consumption. At Ancker Hospital these measures, along with contagious technic in the tuberculosis department, are to be established for a trial period of at least two years, during which I shall continue the tests and examinations described previously to note any change in the incidence of tuberculous infection and disease. An attempt is also being made to reduce the time each nurse spends in the tuberculosis department.

The roentgenograms of the chests of the Ancker group were studied and compared with the results of cutaneous tests. This inquiry was not wholly satisfactory, because in a film taken with the usual technic root shadows are notoriously variable, and the presence of calcification is not always certain. In two instances calcified foci in the parenchyma were noted in nurses giving a 3 plus. Ten nurses showed diaphragmatic adhesions, five of the nurses gave positive reactions and five did not. Two parenchymatous infiltrations were noted, one positive and one negative which later became positive (case 4). The nurse with the parenchymatous lesion and positive skin test was permitted to continue working, as she was free from symptoms, the lesion has faded gradually to the point of being barely perceptible. I have begun to make repeated roentgen examinations of nurses who originally gave negative reactions as their reactions become positive, to see whether a childhood type of lesion develops. This investigation will be reported on later, so far it has revealed little, if anything.

The incidence of tuberculous disease among nurses has not been clearly established. In 1925 Britton and Bollman¹² stated that 2.2 per cent of all nurses employed in Chicago had tuberculosis. Heimbeck¹ found that 12 per cent of student nurses over a period of four

¹² Britton, J. A., and Bollman, E. B. *Tr. Nat. A. Prev. Tuberc.*, 1925.

years developed the disease Shipman and Davis³ found that 26 per cent of nurses in the University of California Training School developed tuberculosis over a period of six years In the Eppendorf Hospital, Much¹³ found that the percentage incidence up to 1918 was 1, and that after the war it rose to 4.6 Ross² found that 6 per cent of 800 nurses in the province of Manitoba had developed tuberculous disease over a four year period Against these figures there is the statement of Whitney⁴ "that in the general population even with the very high death rate among young women from tuberculosis only about 1.5 per cent of them may be expected to develop tuberculosis"

What has happened to the 110 nurses who have entered training in the last two years at Ancker Hospital aside from their acquiring tuberculous infection? In 6, or 5.5 per cent, tuberculous disease has developed This incidence is in contrast to the fact that in the other hospitals in St. Paul in which I have made tests no nurses have developed tuberculosis Of the 6 nurses who had tuberculosis, 3 had pleural effusions, 2 parenchymatous lesions of the lungs of the adult type and 1 a lesion of the lower lobe, apparently of the childhood type Five of these 6 nurses gave negative cutaneous reactions to 1 mg. of old tuberculin when they entered training Abstracts of their histories are interesting

REPORT OF CASES

CASE 1—M. F., aged 20, entered training in February, 1928 There was no tuberculosis in the family nor any known contact The patient gave a negative reaction to 1 mg. of old tuberculin injected intradermally in September, 1928 Physical examination and roentgenograms of the chest were negative

The past history was unimportant In January, 1929, the patient began to have pain in the right side of the chest, and shortly afterward she became short of breath on exertion and noticed fever She was admitted to the hospital as a patient acutely ill, and effusion in the base of the right lung was found The cutaneous reaction to 0.1 mg. of old tuberculin was 3 plus at that time Diagnostic thoracentesis revealed serous fluid, no organisms were found Lymphocytes predominated on the smear Inoculation of a guinea-pig gave negative results

CASE 2—M. O'D., aged 21, entered training in September, 1928 There was no tuberculosis in the family nor any known contact The patient gave a negative reaction to 1 mg. of old tuberculin, a physical examination and a roentgenogram of the chest gave negative results

The past history was unimportant In January, 1929, the patient began to have pain in the left side of the chest She continued her work until May, 1929, when she had pain in the right side of the chest with unproductive cough She was admitted to the hospital as a patient acutely ill, and pleural effusion of the right lung was found On admission the cutaneous reaction to 0.1 mg. of old tuberculin was 3 plus The pleural fluid was serous and contained no organisms, lymphocytes predominated on the smear Inoculation of a guinea-pig gave negative results

13 Much, H. Beitr. z. Klin. d. Tuberk. 64: 155, 1926

CASE 3—E C, aged 20, entered training in September, 1928. There was no tuberculosis in the family nor any known contact. The reaction to 1 mg of old tuberculin was negative, physical and roentgen examinations gave negative results.

The past history was unimportant. In December, 1929, the patient began to lose weight. She had frequent colds. In May, 1930, she had pain in the chest. She reported for examination in July, 1930, when a definite parenchymatous lesion was found in the upper lobe of the right lung with a 3 plus reaction to 0.1 mg of old tuberculin.

CASE 4—G S, aged 21, entered training in September, 1929. Her mother died of pulmonary tuberculosis in 1924. One maternal uncle had pulmonary tuberculosis. There was no reaction to 1 mg of old tuberculin. The results of the physical examination were negative, but the x-ray films showed a small parenchymatous lesion in the apex of the right lung.

The past history was unimportant. The patient was admitted to the hospital as a patient in January, 1930, because of fatigue, loss of weight and fever in the afternoon. Roentgenologic indications of tuberculosis increased, the patient gave a 3 plus reaction to 0.1 mg of old tuberculin.

CASE 5—A E, aged 20, entered training in 1929. There was no tuberculosis in the family nor any known contact. The reaction to 1 mg of old tuberculin was negative, the results of physical examination and roentgenograms of the chest were negative.

The past history was unimportant. In April, 1930, the patient began to tire easily, and found that she had a temperature ranging from 99 to 100 F in the afternoon, at no time was she acutely ill. She had a cough, with mucoid expectoration. There were physical signs at the base of the right lung, dullness, breath sounds suppressed and pleural friction. X-ray films showed a diffuse, dense, homogeneous shadow at the lower lobe of the right lung. Thoracentesis did not reveal fluid. The patient showed a 3 plus reaction to 0.1 mg of old tuberculin.

CASE 6—F B, aged 20, entered training in September, 1928. Her maternal uncle had tuberculosis and visited in the home of the patient when she was from 8 to 12 years old. No record of a tuberculin test was made in September, 1928, but in October, 1929, the reaction was positive.

The past history was unimportant. The present illness began about June 5, 1930, when the patient experienced sharp pain in the chest. On July 13 she was admitted as a patient acutely ill, with a temperature in the afternoon as high as 103 F, the cough was unproductive. There were signs of pleural effusion in the left side of the chest. Diagnostic thoracentesis revealed serous fluid which contained no organisms, lymphocytes predominated on the smear. Inoculation of a guinea-pig gave negative results.

In all of the cases reported, the nurses have recovered or are doing so, and at this time it seems that they will be able to complete their training.

Again one notes the substantiation of Heimbeck's¹ report to a large degree. Obviously, at least, as shown thus far, it is in the main those who originally gave negative reactions in whom tuberculous disease develops, in some instances within a very short time after exposure. Certainly, in adults it does not always require many months for tuberculous disease to develop, and it may develop soon after primary infection. Gor-

don and Cashman,¹⁴ Norris and Landis,¹⁵ Ross,² and others have expressed the belief that tuberculosis does not develop among nurses doctors and other employees who are working in tuberculosis institutions, but this is happening to nurses at Ancker Hospital, and it is stretching one's credulity too far to assume that in this respect Ancker Hospital is unique among American institutions

It is interesting to speculate why the six women became ill. They are from a group which, for its age, is as well controlled as possible, and which has a very uniform environment for over three years. Two came from families with tuberculous histories (cases 4 and 6). All were apparently healthy and robust without serious past illnesses. They worked the same number of hours in an identical occupation, ate the same kind of food and slept in similar quarters as the nurses who did not become ill. Krause and Willis¹⁶ have stated that "under certain circumstances frequently repeated specific reinfection does depress both allergy and immunity" and that "specific intoxication is a potent factor in unfavorably influencing immunity." They also believe, "there is a dosage of reinfection and a spacing of intervals between reinfections one of which is always correlated with the other which are favorable for the highest development and increase of allergy and immunity—but there is also a dosage and a spacing which will depress and (perhaps) destroy each." Is it not probable that the latter type of treatment has been given to the nurses of the Ancker Hospital who have become ill? Is it also not probable that if these women had had an earlier mild infection they would not have become ill? Furthermore, is it not most likely that had these nurses had the protecting advantage of strict medical asepsis, they would have been subjected to fewer and lighter doses of bacilli, thereby escaping tuberculous disease? Of course, factually, one finds oneself confronted with two totally unknown and perhaps unknowable factors—the bacillary dosage that these nurses received and something called individual resistance, which must vary somewhat in each one of us. It is within our power now to control the first factor, perhaps some day in the future we shall be able to define, estimate and enhance the second.

CONCLUSIONS

1 Thirty per cent of the nurses entering Ancker Hospital Training School show positive reactions to the intradermal tuberculin test

2 Practically all nurses at Ancker Hospital show a positive cutaneous reaction to tuberculin before completing training

14 Gordon, B., and Cashman, W. M. Tuberculosis in Workers After Residence in a Tuberculosis Hospital, *J. A. M. A.* **94** 1643 (May 24) 1930

15 Norris, G. W., and Landis, H. R. M. Diseases of the Chest ed. 3, Philadelphia W. B. Saunders Company, 1929, p. 335

16 Krause, A. K. and Willis, H. S. *Am. Rev. Tuberc.* **14** 36, 1926

3 Nurses in five other general hospitals in St Paul reveal an average of 42 per cent reacting positively to tuberculin given intradermally in their last year of training

4 In 6 of 110 nurses, or 5.5 per cent, entering Ancker Hospital in the past two years tuberculous disease has developed, five of them gave negative reactions on entering training and three of them had pleurisy with effusion

5 Tuberculosis sanatoriums and tuberculosis departments of general hospitals should employ rigid contagious technic, especially in those communities in which the incidence of tuberculous infection among young adults is low

6 All patients entering all hospitals should have a roentgenogram of the chest made as a routine procedure

7 All sputums should be sent to the laboratory by nurses

8 It is hoped that studies similar to this one, with the inclusion of medical students, interns and other hospital employees, will be undertaken in other institutions

Drs Elizabeth A Leggett and E G Hubin, Fellows at Pokegama Sanatorium, and Dr F M Feldman rendered assistance during some of the testing

THE ABSORPTION OF GAS FROM ANY CLOSED SPACE WITHIN THE BODY

PARTICULARLY IN THE PRODUCTION OF ATELECTASIS AND
AFTER PNEUMOTHORAX

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The absorption, transportation and elimination of gases in the living body have long been subjects of theoretical interest and extensive investigation. They have now become matters of great clinical importance also. This is especially the case in regard to two conditions which appear at first sight to be diametrically opposed to each other in all essential characters. They are the collapse, or atelectasis, of a lung when a bronchus is closed, and the reexpansion of a lung that has been collapsed by pneumothorax. The forces involved can both inflate and deflate a lung.

It is therefore timely to set forth the mechanics of gas absorption from a lung or from any cavity in the body in which air or any other gas happens to be occluded. In the development of atelectasis the first stage is the complete shutting off and cessation of ventilation in a part or the whole of a lung¹. The air then gradually disappears and produces collapse of the part. In this absorption of gas there is nothing peculiar to the lungs. The same process of absorption acts throughout the entire body, for air, or any other gas, introduced into any cavity or tissue of the body gradually disappears. The same forces that produce atelectasis when a bronchus is blocked induce also the absorption of air or any other gas in a pleural space after a therapeutic pneumothorax. As the gas is absorbed from the pleural space the collapsed lung is drawn outward and thus reinflated. In the one case an occluded lung is collapsed, in the other a collapsed lung is reexpanded. But the forces of absorption of gas are the same in both cases.

GAS PRESSURES IN LUNGS AND BLOOD

Knowledge of the pressures and movements of the respiratory gases of the blood has been won by the arduous labors of many investigators.

* Submitted for publication, April 17, 1931

* From the Laboratory of Applied Physiology and the Sloane Physics Laboratory, Yale University

1 For references to the literature, see Henderson, Yandell. Acapnia as a Factor in Postoperative Shock, Atelectasis and Pneumonia, J A M A 95 572 (Aug 23) 1930

Pflüger, Bohr, Haldane, Barcroft, Hasselbalch, Haggard and Henderson, Van Slyke and others, and is one of the most highly developed fields of physiology² In the main these investigations have traced the behavior of the gases in normal respiration, but the knowledge won may be applied to abnormal processes as well The main points involved are as follows

In normal air at sea level there are approximately pressures of 160 mm of oxygen, 600 mm of nitrogen and 0.3 mm of carbon dioxide Each of these components is termed the partial pressure of the particular gas Their sum total, plus a variable amount of water vapor, is the barometric pressure, which at sea level varies around 760 mm

During normal breathing there are in the alveolar air of the lungs (partial) pressures of about 100 mm of oxygen, 40 mm of carbon dioxide, and 570 mm of nitrogen, plus 50 mm of water vapor As air passes freely in and out of the lungs, the total gas pressure in the alveoli is necessarily that of the outside air 760 mm The blood flows from the lungs to the left side of the heart and on into the arterial system containing oxygen, nitrogen and carbon dioxide at almost exactly the same pressures that these gases have in the lungs

In the tissues the blood loses oxygen and takes up a somewhat smaller amount of carbon dioxide, depending on the respiratory quotient at the time But as the blood holds these two gases by two distinct mechanisms—oxygen combined with hemoglobin and carbon dioxide largely as sodium bicarbonate—the pressure of oxygen is lowered much more than that of carbon dioxide is raised Indeed, owing to the interaction of these gases in the blood (the Bohr-Haldane reciprocal effects), a considerable amount of carbon dioxide may be taken up with little or no increase of its pressure, if there is simultaneously a considerable decrease of the oxygen content of the blood

For these reasons the venous blood returns to the lungs with its oxygen at the approximate pressure of only 40 mm—a lowering of 60 mm below the pressure of oxygen in the arterial blood The pressure of carbon dioxide is simultaneously increased, but to a much less extent, rising only 6 mm or less It is 40 mm in the arterial blood and 46 mm or less in the venous The pressure of nitrogen is unchanged, 570 mm in both arterial and venous blood The pressure of water vapor is also unaltered at 50 mm, as it is determined solely by the temperature

2 For reviews of the literature, see Haldane, J. S. *Respiration*, New Haven, Conn., Yale University Press, 1922; Henderson, Y., and Haggard, H. W. *Noxious Gases and the Principles of Respiration Influencing Their Action*, American Chemical Society Monograph Series, New York, Chemical Catalog Company, 1927; Campbell, J. A. *Gas Tensions in the Tissues*, *Physiol. Rev.* **11**: 1 (Jan) 1931

The total of the pressures ($40+46+570+50$ mm) for venous blood is thus only 706 mm, while the total alike for the arterial blood, the alveolar air and the air pressing on the body from without is 760 mm. This decrease of total gas pressure of about 54 mm in the venous blood, due to the exchange of oxygen and carbon dioxide, plays an essential part in the normal process of respiration. It is also the factor which prevents the development or maintenance, except temporarily, of any gas-filled space in the body. This difference of gas pressure induces the absorption of gases from the pleural cavity in pneumothorax. Unfortunately it is also a factor of critical importance in the production of atelectasis in any portion of the lung which for a time is not ventilated.

As the total gas pressure in the venous blood is always less than that of the outside air, it is impossible for occluded gas in any part of the body ever to come into such equilibrium with the venous blood that it continues unabsorbed. To be in equilibrium the total pressure of the occluded gases would have to be only 706 mm. But the pressure of the outside air acting through the soft tissues of the body compresses any gas-filled space until its pressure is 760 mm. The total gas pressure in the space is then about 54 mm higher than the total gas pressure in the venous blood flowing through the tissues surrounding it. This difference of gas pressure leads to absorption, more or less rapid, depending on the solubility and diffusibility of the various gases.

THE PROCESS OF GAS ABSORPTION

The details of the process of absorption in the development of atelectasis are, however, somewhat more complicated than this general explanation would indicate. As three gases are involved with different degrees of solubility and rates of diffusion through moist membranes, the process of absorption occurs in two distinct stages. During the first stage, immediately after a bronchus is occluded, the oxygen in the alveolar air at a pressure of 100 mm diffuses into the (venous) blood in which the oxygen pressure is only about 40 mm. Simultaneously, carbon dioxide diffuses from the blood into the alveolar air, but in less amount, since the difference of pressure of 6 mm in the blood and in the air is quickly equalized. Only a few seconds are required for the occluded air in this way to lose oxygen to the blood from a pressure of 100 mm to 40 mm, and for carbon dioxide to increase in the air from 40 mm to 46 mm. If the lung were a rigid box there would thus be induced a decrease of total pressure of 54 mm. But, as the lung has a structure which yields readily to the slightest change of pressure, what actually occurs is a decrease of volume.

There is now less gas in the occluded lung than initially and its volume is decreased. But the total gas pressure within it is nearly the same as before. The pressure of the air in the normal lung is 760 mm, and the pressure on the exterior of the body, which is transmitted through the abdominal viscera on the diaphragm, is also 760 mm. The occluded lung therefore shrinks, or is compressed by the pressure in the normal lung and that on the abdomen, until the pressure within the occluded lung is also 760 mm, minus a small force due to the elasticity of the other lung. The first decrease of volume in the occluded space is now complete and a second stage then sets in.

ABSORPTION OF NITROGEN

As nitrogen is much less soluble and therefore diffuses through the membranes of the lung more slowly than the other gases, the amount of nitrogen in the occluded air is at first little changed. But, as the volume of the occluded lung has decreased, the unchanged amount of nitrogen in it is compressed into a smaller space. For this reason the partial pressure of the nitrogen is increased.

The pressure of nitrogen is now 624 mm, which is 54 mm higher than it was originally and 54 mm higher, therefore, than the pressure of nitrogen in the venous blood. It is higher, in fact, by exactly the amount that the sum of the partial pressures of oxygen and carbon dioxide has fallen. The pressures in the occluded lung are then oxygen 40 mm, carbon dioxide 46 mm and nitrogen 624 mm, plus water vapor 50 mm (total 760 mm), while the pressure of nitrogen in the blood is still 570 mm. Under this difference in the pressure of nitrogen in the occluded air and that in the blood, this gas gradually diffuses from air to blood and is carried away by the circulation. As this occurs the pressures of oxygen and carbon dioxide are left a little above those in the venous blood, and these gases also pass from air to blood, for the total pressure in the occluded air is always nearly 760 mm. Meanwhile, owing to the continued absorption of the oxygen from the blood in the tissues, the pressure continues to be only 706 mm in the venous blood flowing through the occluded lung.

This process continues until no gases are left, for the oxygen and carbon dioxide are always slightly, and the nitrogen considerably, above the pressure of each in the venous blood. Meanwhile the barometric pressure of the atmosphere, acting through the open parts of the lung and on the abdomen, presses the mediastinum over and the diaphragm up, until complete collapse of the finally apneumatic lung or lobe results. The alveolar surface and the blood flow are both large, and the absorption is therefore rapid.

If, instead of the air being occluded in a lung, the condition is that of a therapeutic pneumothorax, the air in the pleural space is gradually

absorbed into the venous blood. The collapsed lung is reexpanded simultaneously by atmospheric pressure, provided that the outside air can enter its airways and alveoli freely. But the surface and blood flow in the pleura are less than within the lung, and the absorption is therefore slower.

If, instead of a sea level barometric pressure of 760 mm, the prevailing barometer is considerably lower, as it is in mountain altitudes, the process of gas absorption occurs in essentially the same manner as at sea level. Indeed the oxygen pressure of the venous blood tends to fall even further below that of the arterial blood than it does when the oxygen in the air breathed is at its sea level value. Through the interaction of oxygen and carbon dioxide in the blood the pressure of carbon dioxide is also reduced. The absorption of gas from any occluded space is thus accelerated. This fact may explain why pneumonia commonly assumes a fulminating character in elevated localities.

On mechanical grounds no other mechanism than that actuated by these gas pressures is needed to account fully for the process of gas absorption in an occluded lung or in a pleural space. In the absorption the hydrostatic pressure of the blood in arteries, veins and capillaries, the so-called blood pressure, plays no part whatever. Blood pressures are the means by which the flow of blood around the circulation is induced, but they are not factors in the diffusion of gases.

Not only does the foregoing description fit the requirements of theory, but it is also in accord with a wide range of physiologic and clinical observations by many investigators. In particular it is in accord with the recent observations of Coryllos and Birnbaum³ on the conditions in an occluded lung during the development of atelectasis.

CONCLUSION

The development of atelectasis is explainable on the basis of well established principles of physiology. The forces involved are essentially the same as those that control the diffusion of gases in normal respiration. The same principles and forces account also for the absorption of air from a pleural space after a therapeutic pneumothorax, and indeed for the absorption of gas from any space in the body.

The pressure of oxygen in venous blood is about 60 mm lower than in arterial blood. The pressure of carbon dioxide is only about 6 mm higher in venous blood than in arterial blood. On this account,

³ Coryllos, P. N., and Birnbaum, G. L. Alveolar Gas Exchanges and Atelectasis. The Mechanism of Gas Absorption in Bronchial Obstruction, *Arch Surg* **21** 1214 (Dec.) 1930.

the total gas pressure in venous blood is always considerably less ($60 - 6 = 54$ mm) than the total gas pressure of the atmosphere on the exterior of the body. The pressure of air in the lungs and of the atmosphere on the outside of the body compresses any gas-filled cavity, such as an occluded lung or pleural space, until the total gas pressure within it is nearly the same as that of the atmosphere. This pressure is therefore higher than the total gas pressure in the venous blood. Each gas then diffuses into the blood at a rate dependent on its own partial pressure, its solubility and the capacity of the blood for it.

As rapidly as gas is absorbed, the cavity is compressed by the pressure of the atmosphere on the soft tissues. As oxygen and carbon dioxide are absorbed quite readily, the partial pressure of nitrogen in the occluded air is thus raised above the pressure of this gas in the blood, and it gradually diffuses and is carried away by the blood. The rapidity of absorption is determined by the vascularity and surface area of the part.

In the absorption of gases, blood pressure is not at all involved. The only forces acting are the pressures of the gases in the occluded space and in the blood, and the atmospheric pressure in the normal parts of the lungs and on the exterior of the body.

EXPERIMENTAL AGRANULOCYTOSIS

INFECTION OF RABBITS WITH *SALMONELLA SUIPESTIFER* BY
WAY OF THE BLOOD STREAM¹

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Leukopenia accompanies numerous infectious and toxic conditions. However, the diminution in the number of the white corpuscles is oftentimes only transitory, and the drop in the leukocyte count, although it may have considerable prognostic significance, is not regarded as anything more than a symptomatic indication of a variety of disorders.

Recently, however, a condition has been described in which the outstanding characteristic, persisting until death of the patient, is the disappearance from the circulating blood of the polymorphonuclear leukocytes (granulocytes), the erythropoietic and lymphopoietic systems being but slightly affected. The clinical picture of the disease, as described by various authors, resembles that of a severe infection with fever accompanied by necrotic changes in various mucous membranes, particularly those of the buccopharynx. The patients, in the majority of instances women, not uncommonly develop jaundice. The disease is fatal in about 90 per cent of the cases. Blood cultures during life or post mortem are either sterile or yield various micro-organisms such as streptococci, *B. coli* or *B. pyocyaneus*.

Since Schultz's¹ original description in 1922, the disease has been designated as agranulocytic angina, agranulocytosis, malignant neutropenia or aplastic leukopenia or neutropenia. As stated, pathologic and hematologic investigations, performed on human material, have failed to disclose the etiologic factor of the malady.

In the experiments to be reported, an attempt was made to reproduce in animals a septic disease and to study the possible relationship between the hematopoietic system as seen in agranulocytosis in man and that of this form of sepsis found in the animal.

MATERIAL AND TECHNIC

Full grown rabbits weighing from 1.5 to 2 Kg. were used in the experiments, the animals being fed on oats, hay and small amounts of green vegetables.

¹ Submitted for publication, March 7, 1931.

^{*} From the Medical and Pathological Departments of the Beth Israel Hospital.

1 Schultz, Werner. Ueber eigenartige Halserkrankungen. Gangraneszierende Prozesse und Defekt des Granuloseystems, *Deutsche med. Wchnschr.* 48: 1495, 1922.

Salmonella supester, secured from the American Type Culture Collection, was chosen, first because this micro-organism has been described by some workers² as having a special affinity for the myelopoietic system, leading to a neutropenia of the infected animals, second, because of our intention of inaugurating a study of the hematologic findings in experimental sepsis by the use of a micro-organism that is essentially pathogenic for animals.

The salmonella was grown on plain agar slants, and a twenty-four hour old culture uniformly suspended in physiologic solution of sodium chloride was used in the experiments.

The number of bacteria in the suspension was counted before each experiment, and 1 cc of the solution was injected into the marginal vein of the rabbit's ear. Leukocyte counts and blood smears from the peripheral blood were made at different intervals after the hematogenous infection. The dry films were studied with Wright's stain, preparations also being made with the supravital technic of Sabin. The bone marrow and other tissues were fixed and stained with the customary methods. The animals were killed by air embolus at different intervals after the infection, ranging from five minutes to several days.

EXPERIMENTS

The experiments may roughly be divided into two groups according to the number of bacteria injected: (1) relatively small doses, i. e., between 200,000,000 and 500,000,000 bacteria, and (2) large doses, i. e., between 2,000,000,000 and 5,000,000,000 micro-organisms.

The following is a résumé of protocols illustrative of the entire series of experiments.

GROUP I (relatively small doses)—*Rabbit 169* (fig. 1)—This animal, infected with 200,000,000 organisms, died in four days. Slight leukopenia due to decreases in granulocytes and lymphocytes developed within a few minutes. Immature polymorphonuclear leukocytes began to increase within an hour and reached their peak in three hours and forty minutes, when the leukocyte count was 10,400 per cubic millimeter. After forty-eight hours there was a marked increase in both polymorphonuclear leukocytes and lymphocytes.

The reaction of the monocytes is of interest in this case. In three hours and forty minutes after infection, there was a sudden rise in these cells so that they outnumbered the lymphocytes. In twenty-two hours, macrophages containing phagocytosed erythrocytes could be seen in the blood smears. From that time on their presence in the differential count was considerable, and at the seventy-fifth hour following the infection they made up almost one half of the total leukocytic count, outnumbering by far the lymphocytes. The animal died at the end of the fourth day, although before death there occurred a very marked rise in the following white blood cells: granulocytes, lymphocytes and monocytes. The leukopenia, which developed soon after the infection, was not markedly pronounced, being followed by an increased production of granulocytes and by a marked histiomonocytosis. Examination of the bone marrow after death of the animal showed areas of patchy necrosis involving mostly the granulocytic elements. These areas of degeneration were surrounded by masses of proliferated reticular cells obliterated.

² Lewis, Paul A., and Shope, Richard E. The Blood in Hog Cholera, *J. Exper. Med.* **50** 719, 1929.

ing the normal structure of the marrow (fig 2) The erythropoietic cells and the megacaryocytes were practically unaffected

Rabbit 170 (fig 3) — This animal, infected with 300,000,000 organisms, died six days following the infection. A progressive decrease in white blood cells was noticed, beginning a few minutes after infection, reaching its height at four hours and forty minutes. Reduction in granulocytes was, however, most marked at one hour. On the day following the administration of bacteria, there was a marked rise in granulocytes due to bone marrow activity as evidenced by the marked increase in the number of immature polymorphonuclear leukocytes. At fifty-two hours and in five days there were again decreases in granulocytes, but these were transitory. Just before death, a sudden rise in leukocytes, due principally to the rise in granulocytes, occurred. The lymphocytes were ordinarily diminished during most of the course of the disease. Here, too, as in rabbit 169, the monocytic response became important. Thus, beginning at twenty-two hours, there was a noticeable increase in

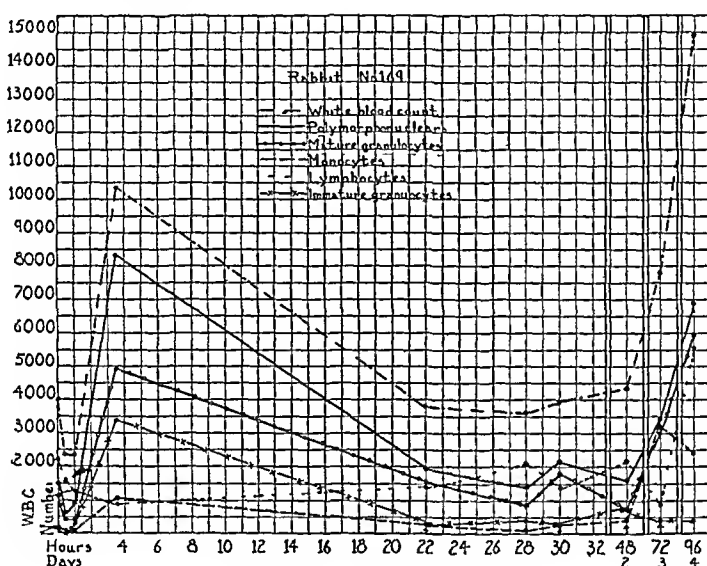


Fig 1 — Blood of rabbit 169

these cells, and in the last two days of the rabbit's illness they tended to outnumber the lymphocytes. On the fifth day following infection, they represented exactly one half of the total number of the white blood cells. Phagocytic macrophages appeared in large numbers during this time. The increase in monocytes and the slight lymphocytopenia were reminiscent of the increased ratio of monocytes to lymphocytes, which has been emphasized by Sabin and her associates³ in infection with tubercle bacilli. Postmortem examination of the bone marrow showed changes not unlike those found in the previous animal.

Rabbit 173 (fig 4) — This animal, infected with 500,000,000 organisms, died eleven days after the infection. There was a rapid fall in the total number of the white blood cells from the original of about 5,000 to 2,000 per cubic millimeter in two hours and thirty-five minutes. This was due chiefly to a fall in granulocytes, although the lymphocytes also became reduced. At three hours and fifty minutes there was a sudden increase in immature polymorphonuclear leukocytes which

3 Cunningham, R. S., Sabin, F. R., Sugiyama, S., and Kindwall, J. A. The Role of the Monocyte in Tuberculosis, *Bull. Johns Hopkins Hosp.* **37**: 231, 1925.

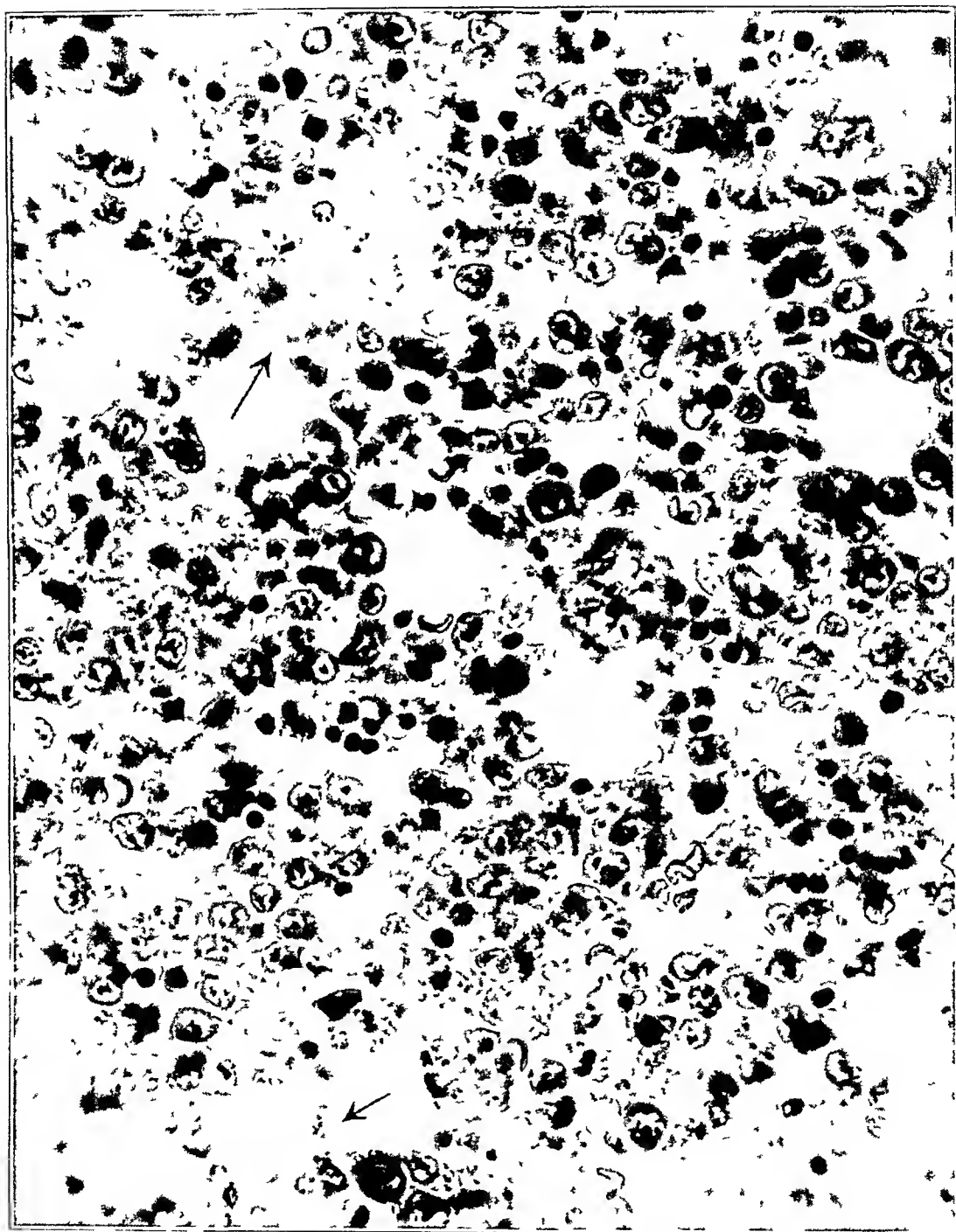


Fig 2—Small areas of necrosis of the bone marrow (indicated by arrows) surrounded by proliferated reticular cells. The erythroblastic tissue and the megakaryocytes are not affected. Hematoxylin and eosin, $\times 600$

reached its peak in five hours and twenty minutes. This resulted in an increase in the total number of the white blood cells. At twenty-four hours, however, there was evidence that the granulocytes were again becoming diminished, and at forty-eight and seventy-two hours, respectively, there was a marked diminution in these cells. At twenty-four hours, monocytes and histiocytes became markedly increased, so

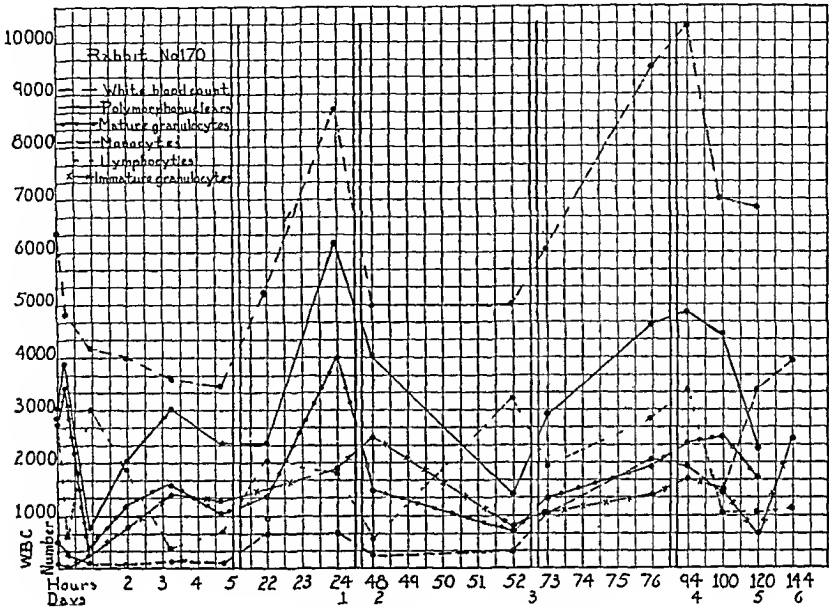


Fig 3—Blood picture of rabbit 170

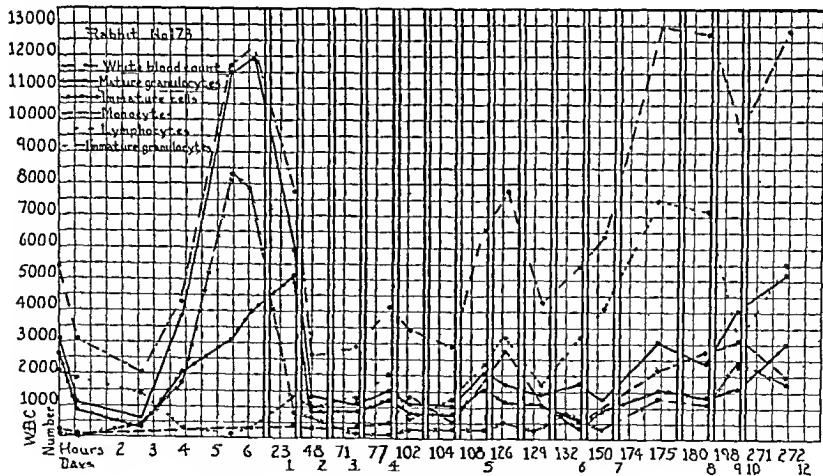


Fig 4—Blood picture of rabbit 173

that at times during this period they outnumbered the lymphocytes. The latter cells, which had been normal or somewhat reduced in number, became definitely increased in number beginning with the fifth day following infection, reaching their peak on the seventh day. On the twelfth day following infection, the animal died, the leukocyte count being fairly high and all the leukocytic elements being well represented. Postmortem examination of the bone marrow showed islands of necrosis of the leukopoietic elements.

Rabbit 181 (fig 5) —This rabbit was infected with 100,000,000 micro-organisms. It recovered from the infection and was observed over a period of twenty days. One hour after infection there was a marked fall in the white blood cells due mainly to a decrease in the granulocytes, although the lymphocytes also were diminished. This was followed by an outpouring of immature polymorphonuclear leukocytes after two hours, resulting in a marked rise in the white blood cells. Again on the second day, a secondary fall in the white count took place due chiefly to diminution in granulocytes. Monocytes began definitely to increase in about six hours and from that time represented a large factor in the differential count, out-



Fig 5—Blood picture of rabbit 181

numbering the lymphocytes at various times from one hundred and twenty hours on. Lymphocytes began to increase consistently after the first monocytic rise, finally reaching a fairly constant level of 5,000 per cubic millimeter. In this animal there was first leukopenia due to granulocytopenia and lymphocytopenia. This was followed by an increase in immature polymorphonuclear leukocytes, resulting in a normal or an increased count of the white blood cells which in turn was followed by an increase in monocytes and finally by an increase in lymphocytes.

Summary—The animals of this group, given a relatively small dose of bacteria, developed an initial leukopenia and granulocytopenia within three hours. This was soon followed by an outpouring of immature

granulocytes and in about twenty-four hours by a marked increase in monocytes and histiocytes. The latter frequently contained phagocytosed material. Lymphocytosis developed after several days. The animals died usually in from four to eleven days after infection, one animal remaining alive after twenty days. Postmortem examination of the bone marrow showed patchy areas of necrosis with areas of proliferation.

GROUP II (large doses) —*Rabbit 164* (fig 6) —This animal was given an injection of 2,000,000,000 bacteria and killed about thirty minutes after the infection. Within a period of twenty minutes, the original count of 4,500 white cells per cubic millimeter dropped to 1,400 per cubic millimeter. A differential count of the white corpuscles revealed that at this time the granulocytes numbered 182 per cubic millimeter, as compared with the original count of 3,150 per cubic millimeter.

Rabbit 165 (fig 6) —This rabbit was given an injection of 4,000,000,000 microorganisms and killed about twenty minutes later. Counts made before the injection

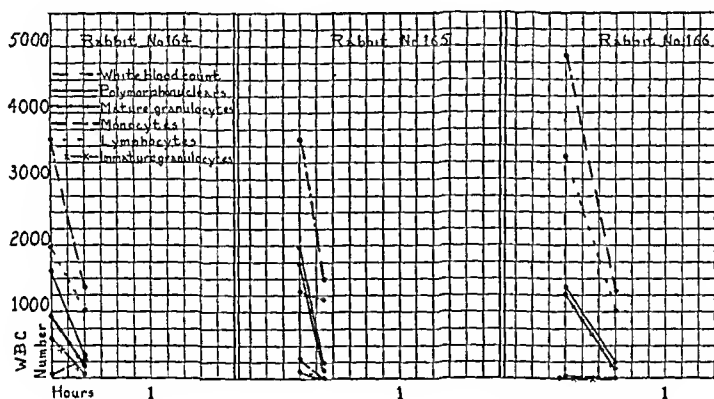


Fig 6 —Blood picture of rabbits 164, 165 and 166

showed that the leukocytes numbered 3,600 per cubic millimeter with 1,944 granulocytes. Fifteen minutes following the infection, the white cell count was 1,500 per cubic millimeter with only 285 granulocytes. There was no change in the number of lymphocytes.

Rabbit 166 (fig 6) —This animal was inoculated with 5,000,000,000 bacteria and killed about forty minutes later. Before injection, the total white cell count of this animal showed 4,800 leukocytes with 1,368 granulocytes per cubic millimeter. Within thirty minutes after injection there occurred a sharp fall of the leukocytes which numbered only 1,300 per cubic millimeter, the granulocytes had almost entirely disappeared from the circulation, and there also was some diminution in the number of the lymphocytes.

Rabbit 174 (fig 7) —This animal was given an injection of 5,000,000,000 bacteria. The normal count of 8,200 white cells per cubic millimeter dropped to 4,200 within forty-five minutes, and the preinjection count of granulocytes of 3,854 per cubic millimeter fell to 2,500. Seventy minutes after the injection, there was halving of the normal white cell count, and the granulocytes numbered 840 per cubic millimeter. In the following minutes, the leukocytic count was showing

rapid diminution, the total white cell count numbering 1,400 per cubic millimeter with only 415 granulocytes. At this period a few immature granulocytes began to appear in the circulation. There was a very moderate diminution in the number of the lymphocytes.

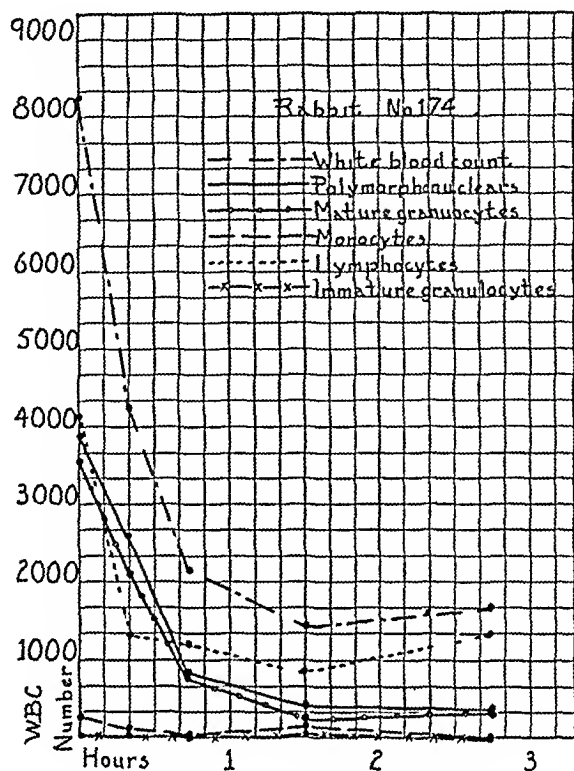


Fig 7—Blood picture of rabbit 174

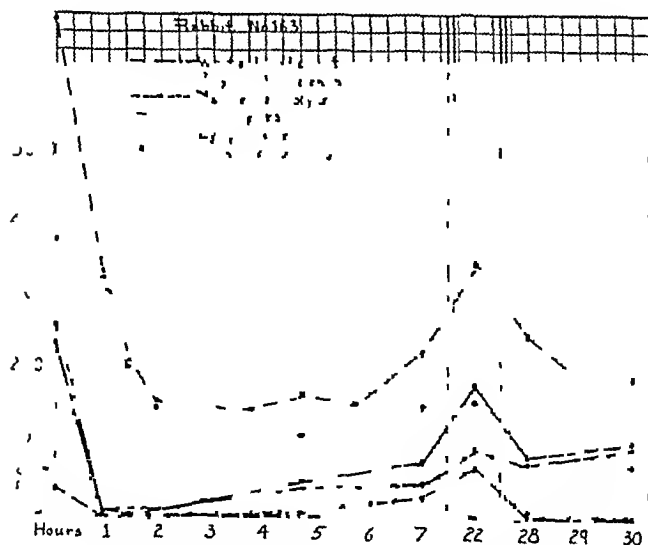


Fig 8—Blood picture of rabbit 163

Rabbit 163 (fig 8)—This rabbit received an injection of 4,000,000,000 bacteria. The normal white cell count was 7,000 per cubic millimeter, the differential count of these showing 40 per cent granulocytes, 55.6 per cent lymphocytes and 4.4 per cent monocytes. Thirty minutes after infection the leukocytic count fell to 3,400 per cubic millimeter, this drop resulting from almost complete disappearance (to 1.5

per cent) of the granulocytes from the circulation. Lymphocytes were present in normal absolute numbers, their relative value being of course high (98 per cent). Eighty minutes after injection the leukopenia was still greater, the white blood cells numbering only 2,200 per cubic millimeter. Only an occasional degenerated granulocyte could be found in the blood smears at this stage. Lymphocytes, too, were beginning to be diminished in number, whereas the monocytes were altogether absent in the circulation.

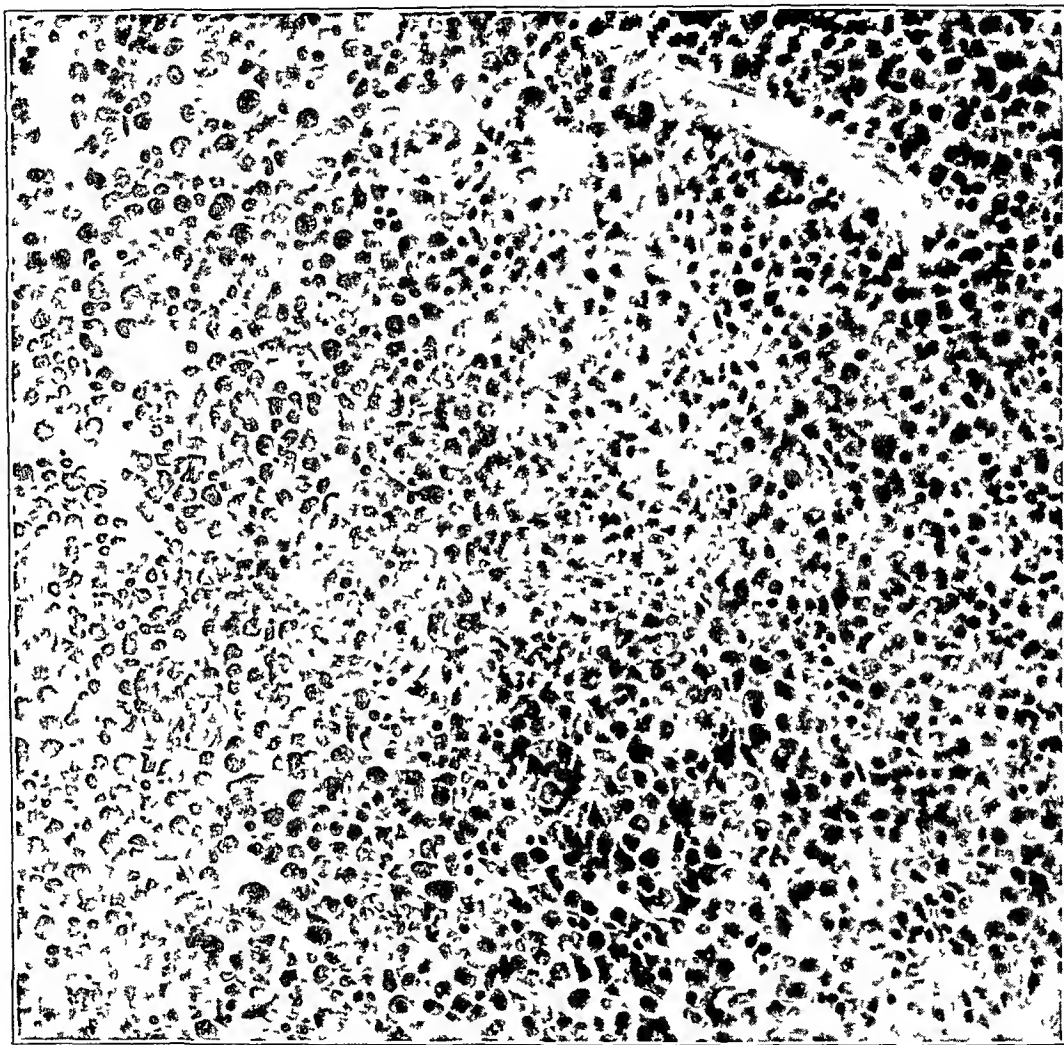


Fig 9—Patchy necrosis of the bone marrow with no pathologic changes in the erythroblastic tissue. Hematoxylin and eosin, $\times 300$

Two hours after the infection, the leukocyte count was very low, 1,025 per cubic millimeter, the relative proportion between the white cells being practically unchanged. The lowest leukocytic count (1,500 per cubic millimeter) was noticed three hours and forty-five minutes after the infection. The first rise in white cells took place about five hours after the infection, at which time the white blood cell count equaled 1,725 per cubic millimeter with a granulocytic count of 30 per cent. There was no appreciable change within the next hours. At twenty-two hours the number of the white cells had risen to 3,600 per cubic millimeter, and there was

evidence of a beginning regenerative attempt on the part of the bone marrow, thus of 52.5 per cent of granulocytes, 24.5 represented immature forms. Of the leukocytes seen at this period in the circulation, about 8 per cent had the appearance of plasma cells. It is interesting that at this time the granulocytes began to show marked "toxic" changes, as evidenced by vacuolization of the cytoplasm and complete disintegration of the cell body. The foregoing rise in leukocytes was, however, transient. At twenty-eight hours, the leukocytic count revealed only 2,600 per cubic

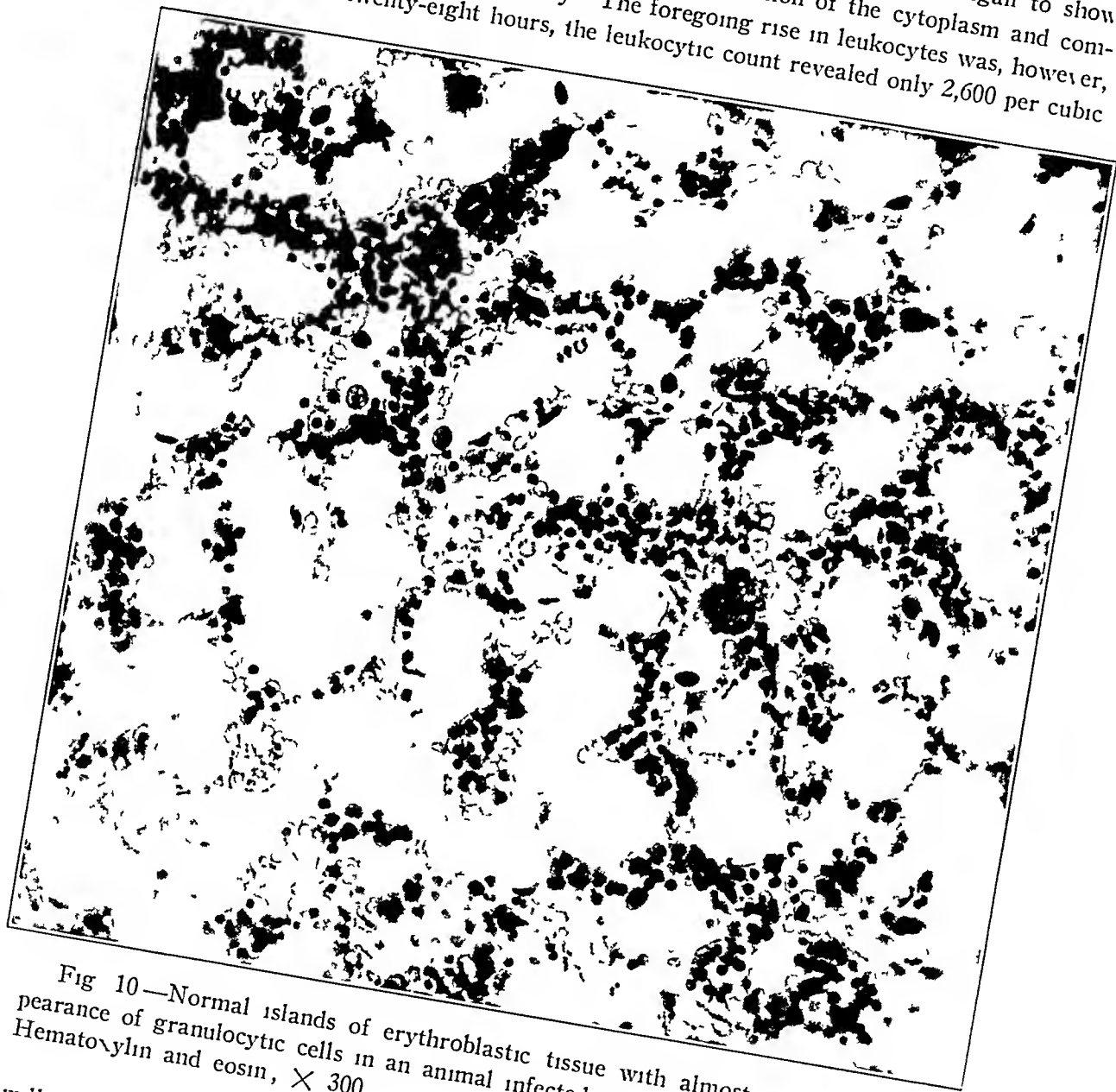


Fig 10—Normal islands of erythroblastic tissue with almost complete disappearance of granulocytic cells in an animal infected with a large dose of bacteria. Hematoxylin and eosin, $\times 300$

millimeter with very low counts of the granulocytes. Monocytes, which had not been seen in the circulation during the entire period of infection, began at this time to appear in the blood, numbering about 5 per cent of the total white cell count. Most of them were of the histiocytic variety. Postmortem examination of the bone marrow revealed a marked necrosis confined to the leukopoietic system. However, even in the presence of this marked infection, areas of normal and regenerating marrow could be seen in places (figs 9 and 10).

Summary—These animals, infected with an overwhelming dose of bacteria, rapidly developed severe leukopenia and almost complete agranulocytosis. There was but little tendency toward regenerative activity on the part of the granulocytes, and monocytosis did not develop to any appreciable extent. The animals died usually within forty-eight hours after infection. The bone marrow, post mortem, usually showed but little evidence of regenerative activity.

COMMENT

It may be seen that under the conditions of our experiments the reaction of the granulocytic (myelopoietic) apparatus was closely related to the gravity of the infection. Thus animals infected with small doses of micro-organisms (figs 1, 2, 3, 4 and 5) in which the infection was left to run its natural course lived for four, six, eleven and twenty days, respectively, following inoculation, animal 181 surviving the experiment, being well after twenty days. Although the time of appearance of the lowest leukocytic and granulocytic counts varied among individual animals from fifteen minutes to four hours and forty minutes, the average time was two hours. However, definite evidence of a marked increase in the production of granulocytes was seen in from three to four hours. It may be said that the time for the appearance of large numbers of immature polymorphonuclear leukocytes, which at times reached the figure of from 8,000 to 9,000 per cubic millimeter, was surprisingly constant, varying within the narrow limits of three and four hours. This increase in immature granulocytes resulted, of course, in a marked increase in the total number of the white blood cells. This group of animals was distinguished from the others, not only by the longer course of the disease, but chiefly by the marked monocytosis they developed. An increase in monocytes, which was generally associated with the presence of histiocytes as well, took place in from four to twenty-four hours following the inoculation, reaching its peak in from fifty-two to one hundred and forty-four hours after infection. At this period monocytes sometimes outnumbered lymphocytes, being present in numbers varying from 3,000 to 8,000 per cubic millimeter. It is interesting that once the monocytic rise was at its peak, this tended to be maintained, so that the monocyte-lymphocyte ratio was often 1 or even over 1. At this period of the infection, intensely phagocytic macrophages could often be seen. At the height of the monocytic rise there also occurred a sharp increase in lymphocytes, this taking place in from fifty to one hundred and seventy-four hours following the infection. However, this lymphocytosis had a tendency to diminish during the course of the disease.

The blood picture in this group of animals can therefore be divided arbitrarily into five stages (1) stage of leukopenia, due to diminution in granulocytes and lymphocytes, (2) stage of marked increase in immature granulocytes, (3) stage of monocytosis and histiocytosis, (4) stage of lymphocytosis, and (5) stage of normality

The duration of the disease in rabbits that received large doses of bacteria was about forty-eight hours. In these animals leukopenia resulting from a granulocytopenia developed within a short period, varying from fifteen to thirty minutes following the infection. The total white blood cell count after infection never rose above 3,600 per cubic millimeter, being generally below that figure. In an occasional instance granulocytes were reduced to the low figure of 22 per cubic millimeter. Immature forms of granulocytes never rose above 800 per cubic millimeter. There was at no time a rise in either monocytes or lymphocytes. Likewise no changes were observed in the red cells. In brief, only the first of the stages, that is, of leukopenia (neutropenia) without any signs of regeneration, was present in the blood of this group of animals during the entire course of their illness. The pathologic changes found in the visceral organs resembled those seen in sepsis in general. In the bone marrow, changes were obvious even in those animals that were killed thirty minutes after the infection took place. As in persons with agranulocytosis, the disease was apparently confined to the myelopoietic system only, as evidenced by various degrees of degeneration and wide areas of necrosis. Islands of normally appearing normoblasts could often be seen surrounded by necrotic leukopoietic tissue. The megacaryocytes, too, showed no appreciable changes.

In summary, a relatively small dose of bacteria produced a slight leukopenia followed by an intense regeneration in the bone marrow (fig 11), this being followed by a histiomonocytosis in the circulating blood and later by a lymphocytosis. With a moderately large dose of bacteria, leukopenia, which was not very intense, developed more quickly. Usually a slight regenerative activity was seen and at times a slight monocytosis. An overwhelming dose of micro-organisms brought about a very rapid leukopenia resulting from an agranulocytosis with areas of necrosis of the bone marrow. No regeneration of bone marrow (fig 12) occurred up to the death of the animal.

Are there any similarities between agranulocytosis as seen in man and that resulting from sepsis in the rabbit?

In human beings, as noted in the introductory paragraphs, the disease agranulocytosis (Schultz) is characterized by (1) clinical signs, such as necrosis of the gums, tonsils, buccal and gastric mucosae, vulva and vagina, (2) a hematologic picture evidenced by the diminution or almost

complete disappearance of granulocytes from the circulation, and (3) the absence of a hemorrhagic diathesis. It is characteristic in that the etiology of this disease is unknown, it being thus included in the category of "essential" malignant neutropenia. Schultz was of the opinion that agranulocytosis is a disease per se, being caused by a specific agent that has a particular affinity for the myeloid system. Other

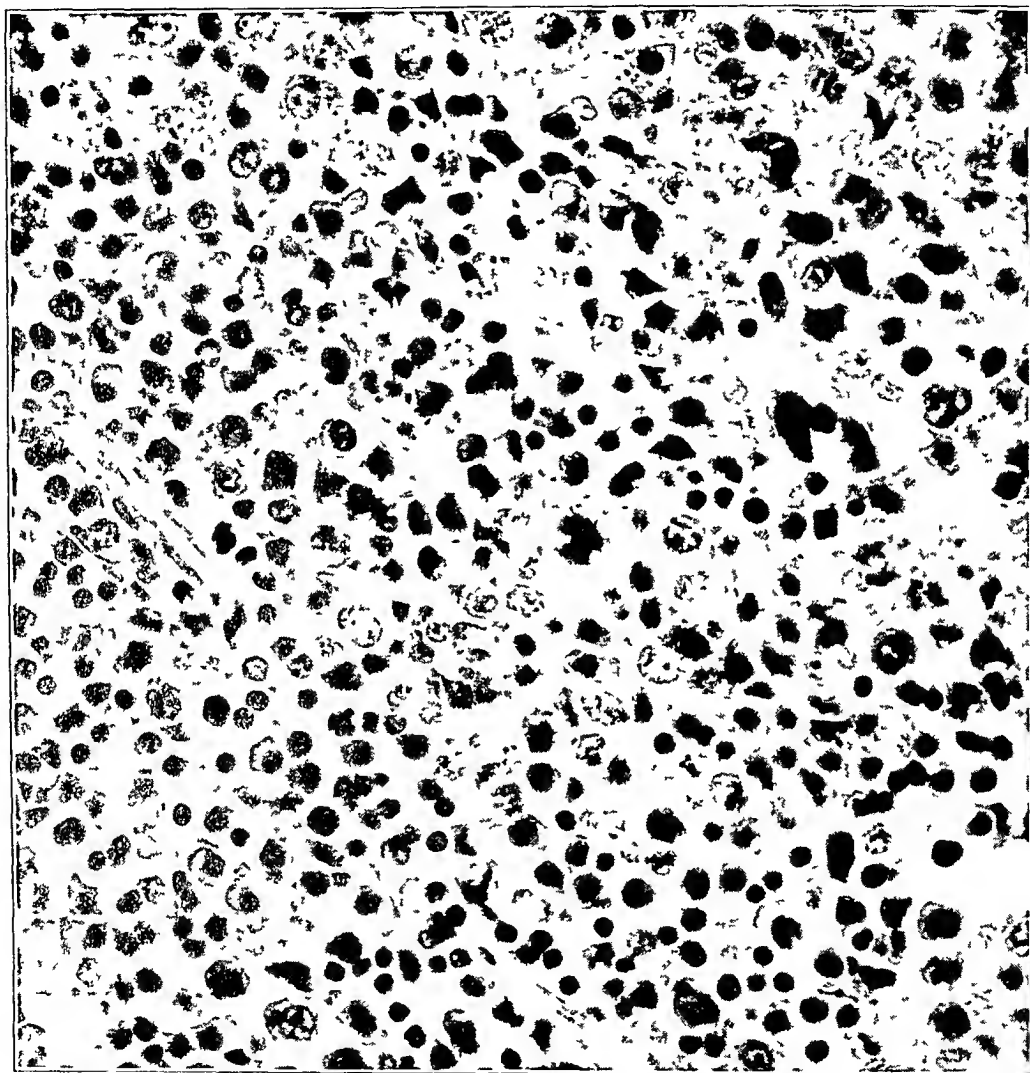


Fig 11—Intense regeneration of bone marrow at the border of a necrotic area. There are no pathologic changes in the erythrocytic elements. Hematoxylin and eosin, $\times 600$

workers regard the malady as a symptom complex of which sepsis is the underlying condition. The hypothesis also has been expressed that it is a form of hyperergic inflammation (allergy) in which the bone marrow is the locus minoris resistentiae. This hypothesis will not be considered here since the study was performed on normergic (anergic) animals.

Remaining to be discussed are (1) the necrotic changes of the mucous membranes and (2) the hematologic picture

As referred to, the condition was isolated as an "entity" because in addition to the agranulocytosis there occurred a necrotizing process in the mucous membranes which was said never to happen in other diseases. However, as has also been noted by other writers,⁴ necrosis

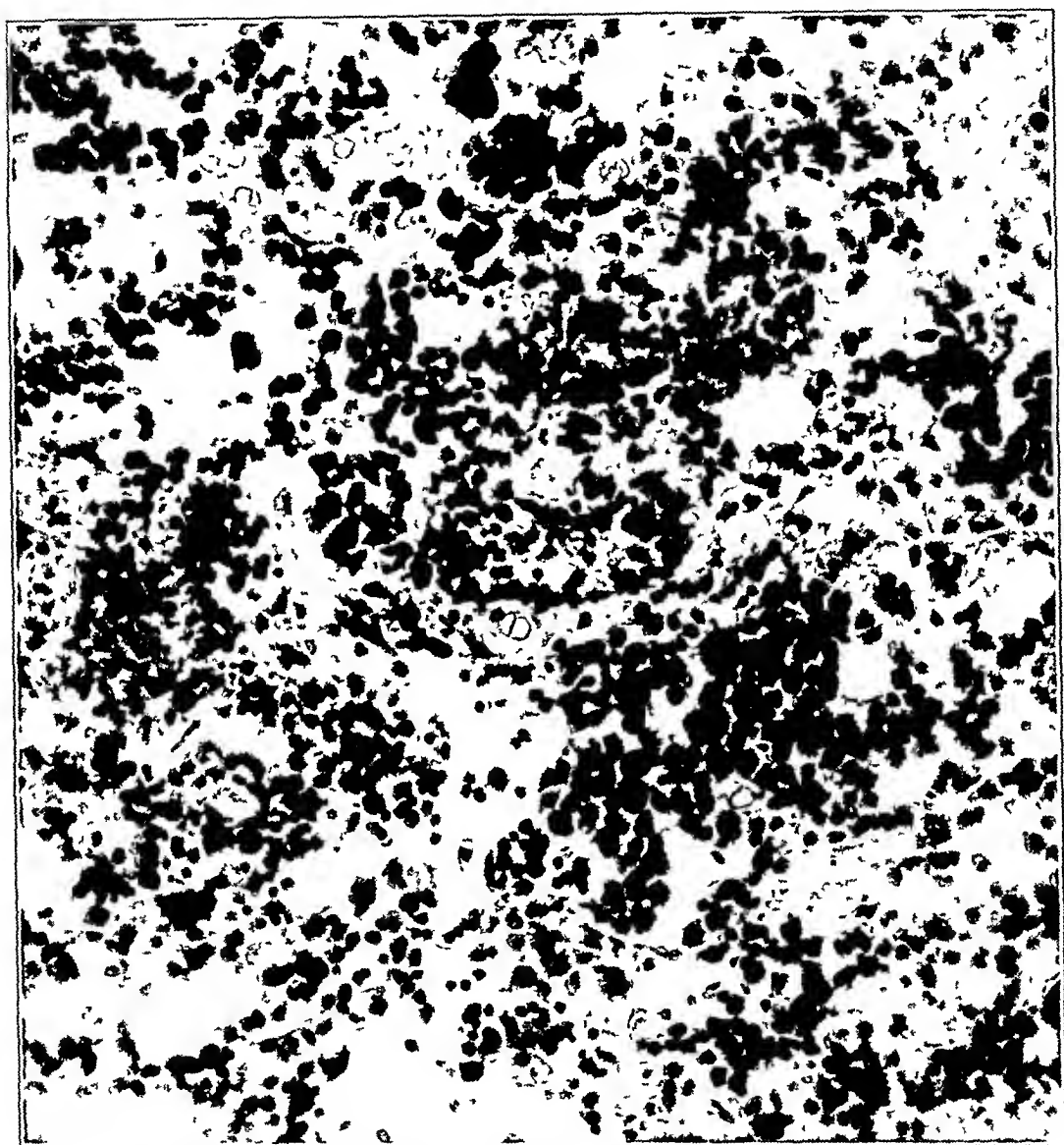


Fig 12—Focal necrosis of bone marrow. Hematoxylin and eosin, $\times 300$

of the buccopharyngeal mucosae occurs in other maladies such as acute leukemia, hemorrhagic diathesis and also sepsis.

Moreover, it has been observed that the occurrence of typical cases of agranulocytosis is not necessarily accompanied by necrotizing

⁴ Barta, T., and Eros, G. Sepsis und Blutbildung, *Virchows Arch f path Anat* **272** 313, 1930. Blumer, G. Agranulocytic Blood Picture in Conditions Other Than Angina, *Am J M Sc* **179** 11 (July) 1930.

lesions of the mucous membranes. Thus, in a series of patients studied at the Beth Israel Hospital,⁵ two patients with a characteristic clinical course and a hematologic picture of this disease failed to show necrosis of mucous membranes. One patient developed necrosis of the cutaneous tissues in the antecubital fossae of the arms following a needle puncture. The history of this patient is as follows:

A woman, aged 41, who had been an invalid for several years, developed an acute infection of the upper respiratory tract eight months prior to admission to the hospital. Since that time she had had constant headaches. Two months before entry she had swelling and stiffness of the knees. One week before admission she became very ill with high fever and slight delirium.

At the hospital she showed a lateral nystagmus of both eyes. The lymphopoietic and erythropoietic systems showed no changes. Her leukocytic count varied between 600 and 1,900 per cubic millimeter. The granulocytes gradually disappeared. A specimen of bone marrow taken for biopsy showed almost complete absence of granulocytes, only a few myeloblasts being found. Following a blood transfusion, the incision wound did not heal, becoming thick and edematous. A white sloughing area of necrosis finally developed. Aerobic blood cultures were sterile, but anaerobic cultures showed a streptococcus. The patient died seventeen days after the onset of the illness.

Here, then, is a case of agranulocytosis with characteristic changes in the circulating blood as well as in the bone marrow in which gangrenous lesions of the mucous membranes were absent. In fact, since the original description of this disease, the experience of most writers is that this condition is not as "rigid" as described in the early reports and that this clinical entity abounds in multiple clinical and hematologic nuances.

From a study of the literature and from the cases observed at the Beth Israel Hospital,⁵ we gained the impression that from a clinical standpoint, the disease agranulocytosis can be arbitrarily divided into three main groups. 1. Severe cases like those originally reported by Schultz. In these instances the onset of the malady is sudden, with a chill, high fever and a necrotizing angina, jaundice and albuminuria being frequently present. The blood in these patients shows an extreme degree of agranulocytosis, and the bone marrow reveals widespread necrosis of the leukopoietic system. The disease is rapidly fatal. 2. Moderately severe cases in which the disease is more protracted, occasionally ending in recovery. The blood of these patients shows a very marked leukopenia, with a few granulocytes, and very numerous monocytes and histiocytes. In the bone marrow one finds areas of necrosis and signs of active regeneration of the myelopoietic system. The patients may or may not have necrotizing lesions of their

5 Dameshek, W., and Ingall, M. Agranulocytosis (Malignant Neutropenia), *Am J M Sc* **181** 502, 1931.

mucosae 3 Mild cases of agranulocytosis in which the disease begins insidiously, having a much longer course. In these patients the leukopenia is less intense and the number of granulocytes is higher than in the moderately severe cases. Again the blood smears show that a high percentage of monocytes and macrophages is present in the circulation, which may be regarded as a "recovery stage" (Schilling⁶). The bone marrow, in addition to necrosis, shows a very active power of regeneration of the leukopoietic system. In these cases, too, necrotic lesions of the mucosae may be absent, and the disease ends in most instances in recovery.

It may be seen then that necrotizing lesions of the mucosae may be present in diseases other than agranulocytosis, and that in this disease the lesions of the mucosae are not a *conditio sine qua non*.

In analyzing the hematologic findings in the animals in our experiments, we find striking similarities between the agranulocytosis resulting from the infection of rabbits with *Salmonella suispestifer* and that seen in the clinic. Thus the severe cases of the disease in man correspond closely to the reaction seen in the animals of group II which received overwhelming doses of bacteria, causing intense necrosis of the bone marrow without signs of regeneration. There is also a close similarity existing between the "recovery phases" seen in the circulating blood in clinical agranulocytosis and that disclosed in the circulation of rabbits that were infected with relatively small doses of bacteria. Two aspects of these phases of particular interest will be discussed briefly: (1) the occurrence of immature granulocytes in the blood, and (2) the presence of histiocytes (macrophages) in the circulation.

The differential count of the white cells in the present experiments was made according to the method of Arneeth as modified by Schilling. In the modification of the latter, four groups of polymorphonuclear leukocytes are discriminated, namely, mature or segmented forms, band or "stabkernig" forms, young forms and myelocytes. In our study the last three varieties of cells were grouped together as immature polymorphonuclear leukocytes (immature cells in the charts).

The significance of an increase in these cells in the circulating blood following an initial granulocytopenia obviously represents a rapid regenerative activity on the part of the white cells of the bone marrow in response to injury. In the experiments herein presented, this was brought out in the animals that were killed at the height of increase in the number of the immature granulocytes (rabbits 175, 176, 177, 178 and 179). The bone marrow in these rabbits showed, in addition to necrosis, areas of intense regeneration.

6 Schilling, V. *The Blood Picture*, St. Louis, C. V. Mosby Company, 1929.

Paradoxical as it may appear, immature polymorphonuclear leukocytes may be present in increased numbers in the circulation in instances of almost complete necrosis of the bone marrow. It was thought by Schilling that this resulted from the gradual discharge of the remnants of the immature leukocytes of the bone marrow. In these instances a steady decrease in the total number of the polymorphonuclear leukocytes is observed instead of the customary rise in these cells which is found in conditions with regenerative activity of the marrow. These two types of reactions were designated by Schilling⁶ as the "regenerative" and "degenerative" shifts of the white blood cells. It is interesting then that what was advanced by Schilling as a mere hypothesis has been borne out in our experiments (rabbits 163, 171, 167 and 180).

In regard to the histiomonocytosis observed in the blood stream, it is interesting that whereas the monocyte is seen normally in the circulating blood, the histiocyte (macrophage) is present in the circulation only in pathologic conditions.⁷ Simpson⁸ and others were able to induce experimentally an invasion of the blood by these large phagocytic cells, and one of us⁹ (D. Dameshek) observed a marked increase in macrophages in the blood in the convalescent stage of various infectious diseases, in certain chronic infections such as syphilis, and also in the leukemias.

In the present investigation a marked increase in the monocytes and histiocytes (fig. 13) occurred regularly in the blood of those rabbits that received relatively small doses of bacteria (group I). A subsequent study of the tissues of these animals revealed a marked proliferation of the cells of the reticulo-endothelial (macrophage) system. It is thus apparent that the blood was flooded with these cells as a result of the overactivity of the mesenchymal defensive apparatus. The "stage of defense" may, however, be only ephemeral, as can be seen in many of our experiments in which the animals subsequently died. In two patients with agranulocytosis recently observed in the clinics of this hospital, the stage of recovery was likewise accompanied by an invasion of the blood with macrophages which numbered about 60 per cent of the total count of the white blood cells. In these cases the "defense" was apparently efficient since the patients recovered from their illness. This may possibly be due to the fact that (1) experimental infection is as a rule more severe than that observed clinically in man and (2) in experimental inoculation which is performed in

7 Maximow, Alexander A. The Macrophages or Histiocytes, in Cowdry, E. V. *Special Cytology*, New York, Paul B. Hoeber, Inc., 1928, vol. 1, p. 427.

8 Simpson, M. H. The Experimental Production of Macrophages in the Circulating Blood, *J. M. Research* **53** 77, 1922.

9 Dameshek, W. The Appearance of Histiocytes in the Peripheral Blood, *Arch. Int. Med.* **47** 968 (June) 1931.

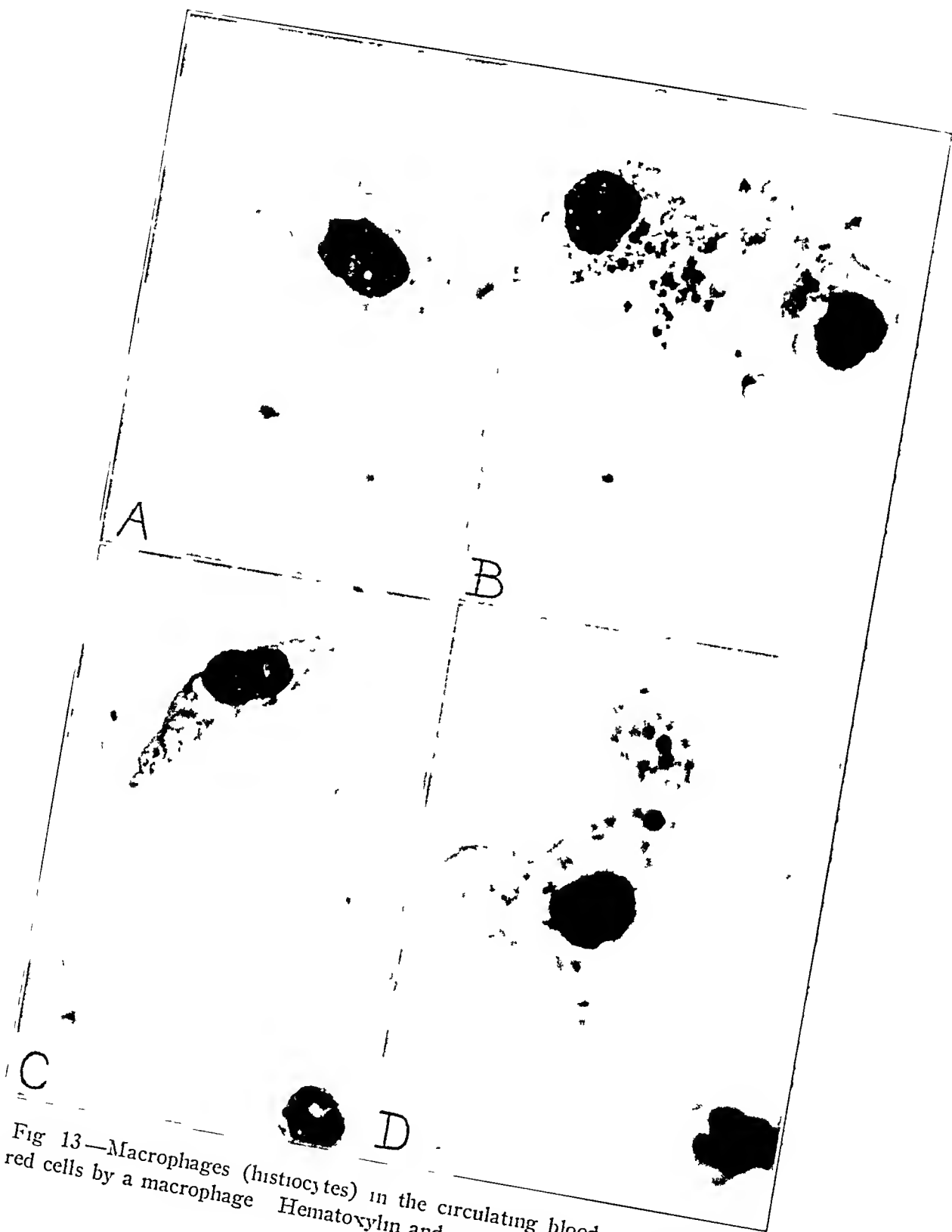


Fig 13—Macrophages (histiocytes) in the circulating blood of red cells by a macrophage Hematoxylin and eosin, $\times 850$ A, phagocytosis

normergic (anergic) animals the "dose" of the infectious material (other conditions being equal) plays apparently the dominating rôle, whereas in man "constitutional" factors as well enter into play

CONCLUSIONS

The purpose of the present study has been to determine the possible similarity between the blood picture as seen in agranulocytosis in man and that found in a form of experimental sepsis in rabbits

The results have shown that there are close similarities between the agranulocytosis resulting from the hematogenous infection of rabbits with *Salmonella supestifei* and that observed in cases of agranulocytic angina in man. Thus, the reaction in severe cases of human agranulocytosis corresponds to that of the animals that received overwhelming doses of bacteria, i. e., a persistent neutropenia and an intense necrosis of the bone marrow without signs of regeneration. A close similarity likewise exists between the "recovery phase" seen in the circulating blood in clinical agranulocytosis and that disclosed in the circulation of rabbits that were infected with relatively small doses of bacteria, i. e., a marked histiomonocytosis.

Incidentally, Schilling's clinical concept of "regenerative" and "degenerative" types of polymorphonuclear "shift" was confirmed by these experiments

SOME IMMUNOLOGIC ASPECTS OF LEUKEMIA

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AND

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PHILADELPHIA

Investigations of Carrel and Ebeling¹ into the proliferative activity of blood leukocytes in tissue cultures have shown that homologous serum possesses a marked antiproliferative effect on polymorphonuclear leukocytes and lymphocytes. The first mentioned type of white blood cell disappears entirely from the culture in a few days and the latter type in from one to two weeks. By a process of physiologic selectivity a pure culture of mononuclear cells remains, which can be kept alive for several months. Carrel and Ebeling concluded from this observation that homologous serum may possess a similar action *in vivo*, because the number of leukocytes would increase indefinitely if serum were not endowed with this property. They added that probably the increase of the growth-inhibiting action of serum in the course of life determines a decrease in the activity of the white cells and modifies their secretions. They suggested, moreover, that possibly this is one of the mechanisms by which the profound changes are brought about by age in blood serum, and that it may be related to certain diseases in this period, such as cancer.

It occurred to us that perhaps a disturbance in the antiproliferative activity of the blood serum might be the cause of the enormous increase of leukocytes in leukemias. The correctness of this supposition required that leukemias should be characterized by a decrease or a lack of the antiproliferative qualities of the leukemic serum allowing an excessive and unimpeded proliferation of leukocytes. To put this theory to a test the effects of normal and of leukemic plasma on the proliferative activity of normal and leukemic leukocytes were studied with the tissue culture method.

EXPERIMENTS

The donor of the leukemic blood was a woman, 53 years of age who had been under clinical observation by Dr E Ellice McDonald for more than a year preceding our experiments. Her spleen was considerably enlarged, extending laterally somewhat beyond the umbilicus and reaching well into the pelvis. Her blood picture at the beginning of our

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* From the Cancer Research Laboratories University of Pennsylvania Graduate School of Medicine

¹ Carrel and Ebeling. *J Exper Med* 36:365, 1922

experiments was as follows hemoglobin, 50 per cent (Sahli), erythrocytes, 3,500,000, leukocytes, 750,000, neutrophilic leukocytes, 50 per cent, myelocytes, 23 per cent, myeloblasts, 6 per cent, lymphocytes, 8 per cent, monocytes, 2 per cent, eosinophils, 7 per cent, and basophils, 4 per cent. The normal blood was taken from a healthy man, 36 years old, with normal observations on the blood. The blood needed for the experiments was obtained by venous puncture, heparin being used as an anticoagulant. The method of Carrel and Ebeling¹ was employed to secure the plasma and the buffy, leukocytic coat. The latter was cut into small pieces which were explanted into a drop of plasma, the slide method of tissue culture being used. There were four sets of *tissue cultures*, each containing twelve slides

- 1 Normal leukocytes in normal plasma
- 2 Normal leukocytes in leukemic plasma
- 3 Leukemic leukocytes in normal plasma
- 4 Leukemic leukocytes in leukemic plasma

The experiments were repeated three times to check the results obtained. These were as follows. It was uniformly observed that the growth and emigration of the normal leukocytes in the leukemic plasma lagged behind those seen in normal plasma cultures during the first twenty-four hours of incubation. This difference became less distinct after forty-eight hours and was negligible thereafter. If leukemic leukocytes were used in this combination, the retarding effect was less marked than in the previous experiment during the first twenty-four hours and was only relatively slight in the forty-eight hour cultures. In the latter observation our results are in agreement with and substantiate those obtained by Hirschfeld².

As the leukemic patient was 53 years of age and the donor of the normal blood only 36 years old, it appeared possible that the difference in growth activity observed might have been caused by the difference in age, resulting in a higher antiproliferative quality of the plasma from the leukemic patient. To exclude this possibility, an identical set of experiments was run, a man 56 years of age being used as the source of normal plasma and leukocytes. The results were the same, but differed somewhat in degree, as the proliferative activity of the normal leukocytes in the normal plasma was not quite so good in this experiment as in the previous experiments in which the blood came from a younger person. The differences in the growth activity of the normal leukocytes in normal plasma compared with that in leukemic plasma were therefore less marked, but still definitely evident.

2 Hirschfeld. *Folia haemat* 34 39, 1927

The conclusions drawn from these investigations are as follows. Leukemic blood does not contain a decreased amount of antiproliferative substance, but has rather a slightly increased amount, if proper consideration is given to the age factor. The enormous increase of leukocytes in leukemias can therefore not be attributed to a disturbance in the physiologic antileukocytic quality of blood serum.

The subsequent qualitative study of the cultures in regard to the type of leukocytes that emigrated from the normal and the leukemic plasma cultures respectively supplied the evidence by which the quantitative differences demonstrated could be properly explained. It was found that the emigration of polymorphonuclear leukocytes was more or less markedly suppressed in the leukemic plasma cultures after twenty-four hours of incubation. As this type of cell disappears normally from the cultures in the course of seventy-two hours, one had to expect that the quantitative differences would decrease after prolonged incubation. This expectation was substantiated by our observations already mentioned. A decreased emigration of polymorphonuclear leukocytes in cultures of normal human leukocytes in leukemic plasma must be regarded as the cause of the quantitative differences observed between the growth activities of these cells in normal and leukemic plasma respectively. The emigration and growth of lymphocytes and monocytes were apparently not interfered with by the plasma of a myeloid leukemia.

Leukemic leukocytes had been cultured previously in normal and leukemic plasma by Aworow and Timofejewskij,³ Hirschfeld² and Parker and Rhoads.⁴ We can substantiate their results and have nothing to add to them. The transformation of mononuclear leukocytes into fibroblast-like cells was especially evident and frequent in cultures of leukemic leukocytes in normal plasma after seventy-two hours of growth.

If we attempt to interpret our observations and try to explain them by processes in the organism which might be responsible for the phenomena observed in the tissue cultures, we are inclined to believe that the massive destruction of myeloid cells in the system of the leukemic patient results in an increase of the antiproliferative qualities of the serum directed against the myeloid cells.

Applying this conception, we attempted to produce an antileukocytic serum by repeated injections of leukemic leukocytes into the veins of the ears of rabbits. The following technic was employed. The buffy coat of 10 cc of venous blood from the leukemic patient was washed in sterile Ringer's solution, to remove the adherent erythrocytes as much as possible, and then ground in a mortar with a small amount of Ringer's solution. When a more or less homogeneous mass was obtained, from 15 to 20 cc of Ringer's solution was added. The suspension had a slightly

3 Aworow and Timofejewskij. *Virchows Arch f path Anat* **216** 184, 1914

4 Parker and Rhoads. *Am J Path* **4** 167, 1928

pink color Immediately after preparation one half of it was injected into the veins of the ears of the rabbit, while the remaining portion was kept in the icebox and was injected three days afterward The first rabbit used received eight injections



Fig 1—Leukemic leukocytes in the plasma of a rabbit given eight injections, twenty-four hour culture, no emigration

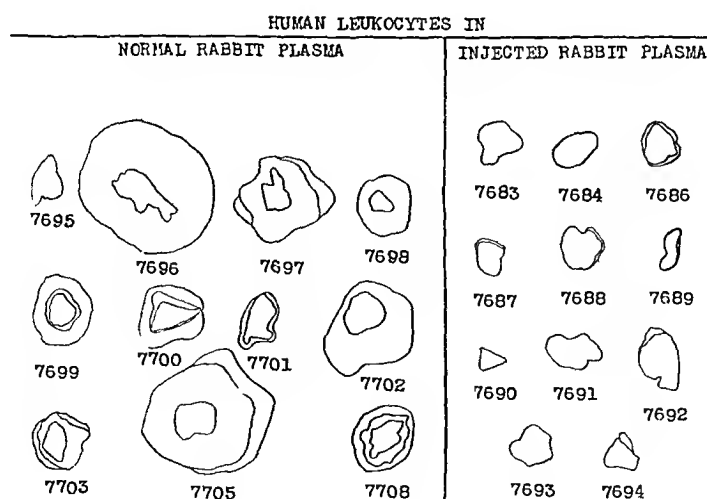


Fig 2—Twenty-four hour cultures traced with the Edinger projectograph

When normal and leukemic leukocytes were cultured in the plasma of the rabbit thus treated, it was seen that the plasma had a marked inhibiting effect on the emigration of leukocytes There was either no emigration or only a very slight one After three days of incubation a

lysis of the plasma around the explant was observed, which was apparently due to the action of proteolytic enzymes freed from the dying leukocytes. There was no evidence of leukocytolysis. Control experiments with leukocytes in normal rabbit plasma showed an abundant leukocytic emigration (fig. 2).

The plasma of the rabbit given injections of leukemic leukocytes had, according to these observations, acquired an antileukocytic quality which proved, however, to be of a nonspecific nature, as not only the emigration of leukemic leukocytes, but also that of normal human leukocytes was impaired.

In a second series of experiments we attempted to determine the antileukocytic titer of the plasma by the tissue culture method, using a rabbit which had received five injections of leukemic leukocytes. The following sets of cultures, each consisting of six slides, were made



Fig. 3—Normal leukocytes in the plasma of a rabbit given five injections, twenty-four hour culture, scanty emigration, with a peripheral ring of agglutinated leukocytes

- 1 (a) Normal leukocytes in the plasma of the rabbit given the injections
(b) Normal leukocytes in normal rabbit plasma
- 2 (a) Normal leukocytes in three parts of plasma from the rabbit given the injections plus one part of Tyrode's solution
(b) Normal leukocytes in three parts of normal rabbit plasma plus one part of Tyrode's solution
- 3 (a) Normal leukocytes in two parts of plasma from the rabbit given the injections plus two parts of Tyrode's solution
(b) Normal leukocytes in two parts of normal rabbit plasma plus two parts of Tyrode's solution
- 4 (a) Normal leukocytes in one part of plasma from the rabbit given the injections plus three parts of Tyrode's solution
(b) Normal leukocytes in one part of normal rabbit plasma plus three parts of Tyrode's solution

The results obtained are as follows. There was a definite impairment in the emigration of leukocytes from the explants in the leukemic



Fig 4—Normal leukocytes in the plasma of a rabbit given five injections, twenty-four hour culture, moderate emigration, with a peripheral ring of agglutinated leukocytes, plasma diluted 50 50 with Tyrode's solution



Fig 5—Normal leukocytes in the plasma of a rabbit given five injections, twenty-four hour culture, good emigration, with a peripheral ring of agglutinated leukocytes, plasma diluted 25 75 with Tyrode's solution

rabbit plasma as compared with the emigration present in the corresponding leukocytic cultures in normal rabbit plasma. This effect decreased in direct proportion to the concentration of the leukemic rabbit plasma present in the medium. There was no emigration evident in 50 per cent of the cultures in concentrated leukemic rabbit plasma. It was moreover, noticed that the emigration zone was much denser in the cultures with leukemic rabbit plasma than in those with the normal rabbit plasma, becoming however less dense with the decreasing concentration of the leukemic rabbit plasma in the culture medium. We observed furthermore that the cultures of the leukemic rabbit plasma showed a sharply defined white ring at the periphery of the emigration zone. The ring consisted of agglutinated leukocytes. The emigration of leukocytes stopped in general rather abruptly at this ring. Leukocytes were only

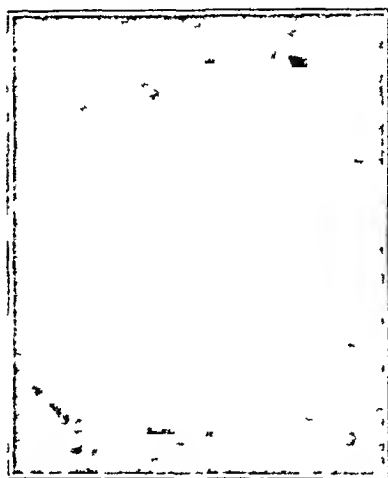


Fig 6—Normal rabbit plasma with normal leukocytes, no agglutination, very good emigration

occasionally found peripherally from this ring in the plasma. The emigration of the leukocytes in normal rabbit plasma was, in strong contrast to the observation just described, abundant and indistinctly defined and seemed to fade away into the plasma.

It is evident from these observations that a rather accurate titration of the antileukocytic qualities of a serum can be obtained by the tissue culture method. Strongly antileukocytic serums will inhibit the emigration of leukocytes completely while weakly antileukocytic serums will allow only a restricted emigration. The toxic effect of the antileukocytic plasma on the cells is evident from the positive nuclear stain especially in the agglutinated leukocytes after the addition of neutral red showing that the majority of the cells in the emigration zone are dead. The great significance of these observations may be demonstrated

by the fact that previous investigators have unsuccessfully attempted to determine the antileukocytic titer of such serums by agglutination, precipitation or complement-fixation reactions, while the existence of a leukocytolysis has never been shown beyond any doubt. These authors used bone marrow (Besredka,⁵ Flexner,⁶ Bunting⁶), spleen or lymph node (Metschnikoff,⁷ Funk,⁶ Flexner⁶), aseptic purulent exudates (after intraperitoneal injections of aleuronat [Gladin⁸] or injections of staphylococcus vaccine [Bierry⁹]) as the source of leukocytic supply. The tissue culture method must be regarded at the present time as the best procedure for the demonstration and titration of cytotoxins. It has been successfully used for this purpose by Lambert,¹⁰ Foot,¹¹ Lumsden¹² and Kimura.¹³

Encouraged by the good results obtained with the antileukocytic plasma in tissue cultures, we gave our patient who had supplied us with leukemic leukocytes several subcutaneous injections of antileukocytic plasma and serum, respectively, in the hope that her blood condition might be benefited thereby. She received in the course of six weeks a total of 30 cc of antileukocytic plasma and serum. The injections caused general discomfort and pain in the region of injection. The spleen decreased somewhat in size, while the leukocytes increased after the first two injections from 470,000 to 700,000 and the erythrocytes from 2,900,000 to 4,000,000. The differential count remained essentially the same. After the second injection the number of leukocytes started to drop and continued to do so until there were (ten days after the last injection) 512,000. The differential count showed at that time a rather moderate shift to the right with an increase of the mature neutrophilic leukocytes and monocytes. The treatment had to be discontinued after the eighth injection on account of the death of the rabbit which had been the source of the antileukocytic serum.

The results so far obtained with the antileukocytic serum in this case allow the following conclusions. The initial rise of the number

5 Besredka. *Die lokale Immunsierung*, Leipzig, 1926.

6 Quoted by Fischer. *Gewebzuechtung*, ed 3, Munich, Mueller & Steinicke, 1930.

7 Metschnikoff. *Ann Inst Pasteur* **14** 369, 1900.

8 Gladin, quoted by Lindstroem. *Acta med Scandinav* (supp no 22), 1927, p 1.

9 Bierry. *Compt rend Soc de biol* **54** 1003, 1902, quoted by Lindstroem (footnote 8).

10 Lambert. *J Exper Med* **14** 453, 1911.

11 Foot. *Centralbl f allg Path u path Anat* **23** 578, 1912.

12 Lumsden. *Lancet* **1** 383, 1924, **1** 112, 1926, *Arch f exper Zellforsch* **6** 206, 1928.

13 Kimura. *Arch f exper Zellforsch* **6** 185, 1927, *Ztschr f Immunitatsforsch u exper Therap* **55** 501, 1928.

of leukocytes was caused partly by the expulsion of leukocytes from the contracting spleen and partly by a stimulating effect of the serum injections on the myeloid tissue. The conclusion as to the latter effect was also confirmed by the appearance of numerous normoblasts in the blood. We had apparently not succeeded in building up a serum in which the antileukocytic qualities outbalanced the normal stimulating action of the serum.

While our results in regard to the therapeutic application of antileukocytic serums were rather discouraging, Lindstroem,¹⁴ whose recent work on this subject came to our attention after our experiments had already reached their final stage, reported such remarkable therapeutic effects of antileukocytic serums in leukemias that the use of properly prepared and titrated antileukocytic serums seems to offer good prospects in the future therapeutic management of these disease conditions. Using a technique similar to ours in the preparation of antileukocytic serums, this investigator succeeded in experiments with various animals (rabbits, cats, monkeys, sheep) in lowering the number of leukocytes in some instances from 8,100 to 50 by the injection of antileukocytic serum. The subsequent examination of the animals dying from the effects of the treatment showed a deficiency of granulocytes in the bone marrow similar to that found in cases of agranulocytosis (Hueper¹⁵). He did not notice the development of a tolerance for, or the production of, antibodies against the antileukocytic serum. Similar observations on the effect of antileukocytic serums on the number of leukocytes in the blood and bone marrow were made by Yamamoto.¹⁶

In a series of eleven patients with myeloid leukemia treated with rather large doses (from 10 to 20 cc.) of antileukocytic serum, Lindstroem was able to produce four complete remissions characterized by a return of the number of the leukocytes to a normal level and great general improvement in the condition of these patients. These remissions lasted for several months. He pointed out that remissions of this character do not occur spontaneously in leukemias nor can they be produced by irradiation or by arsenical medication. An aggravation of the condition following the treatment was observed by him in four cases of advanced myeloid leukemia. He stated that the success of the treatment depends on the therapeutic strength of the serum, which he was unable to determine with the methods available to him. He noted, furthermore, that patients in the early stage of the disease are best suited for the serum treatment.

14 Lindstroem. *Acta med. Scandinav.* (supp. no. 22), 1927, p. 1.

15 Hueper. *S. Clin. North America* **10**: 407, 1930.

16 Yamamoto. *Tohoku J. Exper. Med.* **15**: 324, 1930.

CONCLUSIONS

1 The antiproliferative quality of leukemic plasma is not decreased, but slightly increased, as compared with that of normal human plasma. Myeloid leukemia is therefore not the result of the decrease or absence of this quality of the serum.

2 Myeloid leukemic plasma inhibits the emigration of the granulocytic elements from the explanted clot of blood leukocytes.

3 Antileukocytic serum produced by the intravenous injection of leukemic leukocytes into rabbits impairs the emigrative and proliferative qualities of normal and leukemic leukocytes in tissue cultures.

4 Tissue cultures of leukocytes allow a rather accurate titration of the cytotoxic qualities of an antileukocytic plasma.

5 Isolated favorable therapeutic results (in four of eleven cases) with nontitrated antileukocytic serum in leukemias seem to indicate that properly prepared and titrated antileukocytic serums may offer an effective remissive method for the treatment in leukemias.

AGRANULOCYTOSIS AND HYPOGRANULOCYTOSIS *

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We have applied the term agranulocytosis to the condition in which there is complete or almost complete absence of granular leukocytes, accompanied by leukopenia and relative increase but, in most instances, absolute decrease of lymphocytes. The term hypogranulocytosis, which was first suggested by Weiss,¹ we have applied to that condition in which there is less marked reduction in the number of granular leukocytes and well marked leukopenia, without absolute increase in the number of lymphocytes but with relative lymphocytosis. These terms are not applied to such distinct clinical entities as acute aplastic anemia, acute leukemia with normal or reduced total leukocyte count and agranulocytosis produced by known poisons such as benzene and roentgen rays, for the purposes of this discussion, however, they are applied to the peculiar blood picture associated with various types of infection.

Brown² seems to have been the first to report a case of pharyngeal ulceration with extreme leukopenia, although this fact was overlooked until recently.

Turk,³ in 1907, reported a case of sepsis with complete disappearance of the granular leukocytes, in which at necropsy there was absence of myeloid elements in the bone marrow.

Schultz,⁴ in 1922, reported marked reduction in the number of leukocytes and complete or almost complete disappearance of polymorphonuclears in four cases of necrotic ulcerative infection of the

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¹ From the Mayo Clinic and the Mayo Foundation

1 Weiss, Julius Ueber die gegenseitigen Beziehungen zwischen Schulz'schem Symptomenkomplex (*Mucositis necroticans agranulocytica*) akuter Leukämie und septischem Infekt, *Wien Arch f inn Med* **14** 303 (May) 1927

2 Brown, P K A Fatal Case of Acute Primary Infectious Pharyngitis, with Extreme Leukopenia, *Am Med* **3** 649 (April) 1902

3 Turk, Wilhelm Septische Erkrankungen bei Verkümmern des Granulozytensystems, *Wien klin Wchnschr* **20** 157, 1907

4 Schultz, W Ueber eigenartige Halserkrankungen, *Deutsche med Wchnschr* **48** 1495, 1922

throat to which he applied the term agranulocytosis. Friedemann,⁵ in 1923, reported similar cases which he called agranulocytic angina. Reviews of the literature have been made by Weiss,¹ Kastlin⁶ and Aubertin and Levy.⁷

There has been much discussion in the literature as to the existence of a distinct clinical entity, agranulocytic angina. Schultz⁴ felt that the clinical syndrome to which he applied the term agranulocytosis was a distinct clinical entity, but so many cases have been reported presenting a somewhat dissimilar clinical picture, in which the outstanding feature was agranulocytosis, that the tendency at the present time is to consider the agranulocytosis as a symptom, rather than as a distinct clinical entity.

It is known definitely that certain chemicals, particularly benzene, depress the function of the bone marrow in various degrees, and the effects of thorium X, radium and roentgen rays are equally well known. The lymphocytes are usually affected by irradiation more easily than are the granulocytes, but an overdose of irradiation by any of these means will produce marked reduction of granulocytes and an aplastic effect on the bone marrow.

Farley⁸ reviewed from the literature thirty-nine cases in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. The symptoms varied from those of purpura hemorrhagica to those of severe aplastic anemia and agranulocytosis, depending on whether the principal effect was on the leukopoietic or erythropoietic tissues, on the megacaryocytes or on all of these combined.

Agranulocytosis or hypogranulocytosis conceivably may occur as a result of defective formation of granulocytes, from their abnormal destruction or from their improper distribution or delivery into the circulation. The consensus in the literature is that agranulocytosis usually is due to defective myeloblastic function of the bone marrow, and this is our opinion, but there is some evidence that there is also improper distribution or abnormal destruction. Case 2 is somewhat suggestive of this in the fact that three hours after transfusion the leukocyte count was 300 less than before transfusion. Ordinarily from 500 to 1,000

5 Friedemann, Ulrich. Ueber Angina agranulocytotica, *Med Klin* **19** 1357 (Oct 14) 1923.

6 Kastlin, G. J. Agranulocytic Angina, *Am J M Sc* **173** 799 (June) 1927.

7 Aubertin, C., and Levy, Robert. L'agranulocytose et les syndromes agranulocytaires, *Arch d mal du coeur* **21** 369 (June) 1928, abstr., *Medecine* **9** 469 (March) 1928.

8 Farley, D. L. Depressed Bone-Marrow Function from the Arsphenamins (Including a Type of So-Called Agranulocytosis), *Am J M Sc* **179** 214 (Feb) 1930.

leukocytes for each cubic millimeter of blood should have been added by the transfusion, depending on the leukocyte count of the donor and the blood volume of the patient. This is a single observation and does not prove anything. It may be assumed, although it is not known, that the donor had a normal leukocyte count of from 5,000 to 10,000 cells in each cubic millimeter of blood, it is known that the leukocytes numbered 6,100 at the last examination before the transfusion.

We report fourteen cases^{8a} in which the blood picture was that of agranulocytosis or hypogranulocytosis. Twelve of the patients came under our observation at the Mayo Clinic in the last three years, one was seen by one of us (Dr. Conner) in consultation with Dr. Gilbert J. Thomas of Minneapolis (case 4), and regarding one case there was a telephone consultation with Dr. J. L. Kestel of Waterloo, Iowa, who was acting as consultant with Dr. E. E. Magee of the same city (case 7).

REPORT OF CASES

CASE 1—A woman physician, aged 58, had been a patient at the Mayo Clinic three times in previous years. On March 31, 1928, she came to the clinic stating that in the autumn of 1927 she had had trouble somewhat similar to the present complaint, and had been under the care of her home physician. The nodes on both sides of the neck had been enlarged, and her physician had made a diagnosis of pneumonia, she had been in bed for seven weeks, the nodes gradually had receded to normal size and had been of normal size since. Examinations of the blood had not been made. Ten days prior to her admission at the clinic the nodes in the right side of the neck had been swollen and tender, there had been sore throat and dysphagia, malaise, aching in the muscles and joints, loss of appetite and headache, but no chills, cough or thoracic pain. The highest temperature had been 102.8 F.

At examination, the throat was very red, edematous and swollen, there were enlarged, hard nodes on both sides of the neck, the spleen was not palpable, and there were no palpable nodes elsewhere. On April 3 there was pain in the region of the left breast, and a marked pleuritic rub was found, later bronchopneumonia occurred. On April 6, an abscess developed on the left arm, and later required incision. The temperature varied from 101.5 to 104 F, but gradually receded and was normal on the twelfth day. Cultures from the throat revealed streptococci of the viridans and of the hemolytic types, and staphylococci, but no *Corynebacterium diphtheriae*. Two blood cultures gave negative results. Urinalysis disclosed albumin graded 1 and 2, hyaline casts graded 1 and 2, granular casts graded from 1 to 4, an occasional erythrocyte and pus graded from 1 to 3. The diagnosis was agranulocytic angina and bronchopneumonia. The patient returned home after four weeks and made an uneventful recovery.

The patient was readmitted on June 24, 1928. She had made good improvement and had gained 15 pounds (6.8 Kg). A week before this admission, she had obtained, on her own initiative, roentgen treatment for the nodes of the neck which had not reached normal size. Leukocytes had numbered 2,800 prior to the roentgen treatment, and 1,750, the day after. The day before admission there had been

^{8a} Since this paper was written six additional cases of agranulocytosis have been observed at the Mayo Clinic.

malaise, nausea, vomiting, a temperature of 102 F and tenderness and swelling in the cervical and left inguinal nodes. On admission, leukocytes numbered 1,500, 98.5 per cent of which were lymphocytes and 1.5 per cent, neutrophils. Further results of blood counts are given in the table. There was a questionable pleuritic rub on the left, and some enlargement of the upper cervical nodes and the nodes in both inguinal regions. Later, a node in the right groin underwent suppuration. Still later, an inflammatory condition of the vulva developed. Blood cultures, on June 30 and July 2, contained *Klebsiella pneumoniae* (Friedlander's bacillus). On July 2 and 3, six injections of 10 cc of leukocytic extract were made subcutaneously. The temperature varied from 101 to 104 F until the day of death, when it was 105.5 F by axilla, and the concentration of urea rose to 92 mg in each 100 cc of blood. Before death there was evidence of bronchopneumonia and a suggestion of ileus. Permission to perform necropsy was refused.

Comment—This is a case of undoubted agranulocytic angina (Schultz's syndrome). Although the nature of the attack six months prior to admission is somewhat doubtful, as incomplete observation was made, it seems likely that it was of the same kind as the last two. It is interesting that there was leukopenia five weeks before the patient came under our observation, but that several former blood counts were normal, indicating that the bone marrow was formerly active. The increase in leukocytes and granulocytes soon after development of pneumonia and the abscess on the arm suggest the possibility of using an acute infection therapeutically, for ordinarily such infections are accompanied by leukocytosis. The possible effect of the roentgen treatment of the nodes in bringing on the last attack must be kept in mind. There was no noticeable effect from the use of leukocytic extract. The occurrence of *Klebsiella pneumoniae* in the blood may have been of little significance.

CASE 2—A woman, aged 37, a hospital nurse, came to the Mayo Clinic on Nov 15, 1928. She had first visited the clinic in 1908, for appendectomy, and five times subsequently for keratitis, cough and persistent general debility which never could be attributed to any particular disease. She had been in the hospital on several occasions. There had been mild secondary anemia on several examinations. One week prior to admission the left middle finger had become infected, painful and swollen. Four or five days later, fever, headache, weakness and nausea had occurred. Examination of the blood had been made two weeks before admission, and the number of leukocytes in each cubic millimeter of blood had been found to be 2,000.

At examination, the pharynx and mouth were normal, there were swelling and tenderness in both submaxillary regions, induration of the submental region, some enlargement of the cervical nodes, but none of the axillary and epitrochlear nodes, a slight residual infection of the finger, a few ecchymotic and purpuric areas on the back, a few râles in the base of the right lung and a doubtfully palpable spleen. There were 3,200 leukocytes in each cubic millimeter of blood, 100 per cent of which were lymphocytes. Further counts are given in the table. Three days after admission there developed a sore throat, with no distinct ulceration, and an impetiginous eruption on the face. The patient rapidly became worse, and three days before death an inflamed, indurated area developed on one thigh. A

transfusion of blood was given on November 22. The leukocytes, before transfusion, numbered 500, and three hours after transfusion, 200 in each cubic millimeter of blood. The patient died on November 24 from terminal bronchopneumonia. The diagnosis was agranulocytic sepsis without angina.

At postmortem examination numerous herpetic lesions were found over the face and eyelids. There were some petechiae over the sclerae. The submaxillary glands on both sides appeared to be somewhat swollen. Over the mesial surface of the left thigh there was an indurated area 10 cm in diameter, of purplish color. On section, pus was not exuded. There were numerous petechial hemorrhages over the epicardium. The myocardium was somewhat flabby. The lower lobe of the left lung was of a dark purplish color, its consistency was markedly increased and crepitus could not be felt. The color of the surface after section was diffusely purple, and numerous discrete hemorrhagic areas were seen. There were an excess of bloody fluid and complete absence of air. The lower lobe of the right lung revealed similar nodular, hemorrhagic areas. The mucosa of the pyloric region of the stomach was injected, and there was present what appeared to be a recent ulcer, 1 cm in diameter. In the cecum there were thirty or forty ulcers, some of which were covered by a pseudomembranous exudate. The bone marrow of the diaphysis of the femur was yellow and fatty. The bone marrow was absent from most of the ribs, but some ribs contained red marrow.

The bone marrow from the shaft of the femur was composed essentially of adipose tissue and a prominent reticulum. In the meshes of the reticulum the cells were sparse, they were normal erythrocytes, an occasional nucleated erythrocyte and what appeared to be immature leukocytes. No definite myelocytes or mature polymorphonuclear cells were observed.

The pleura over the lower lobe of the left lung was somewhat thickened. There was marked congestion of the blood vessels. Many of the alveoli were filled with serum and erythrocytes. Some alveoli contained small amounts of fibrin, but there was a striking lack of much cellular infiltration. The cells that were present within alveoli were either lymphocytes or endothelial leukocytes filled with phagocytosed blood pigment. Essentially the same changes were observed in the lower lobe of the right lung, except that there a feeble attempt at organization of the exudate by proliferation of fibroblasts apparently had been made. A section of one of the submaxillary glands revealed edema and necrosis of tissue, particularly in the stroma of the gland and in the connective tissue capsule (fig 1). There was a diffuse, and, in places, a dense cellular exudate composed almost entirely of small lymphocytes and endothelial leukocytes. Polymorphonuclear leukocytes were practically entirely absent. The stomach revealed a number of small ulcers, the bases of which were filled with necrotic tissue and clumps of bacteria (fig 2). The necrosis extended for a variable depth, in places penetrating the muscularis mucosae. In the colon there were numerous small ulcers, there was no inflammatory cellular reaction about the regions of necrosis. The skin of the left thigh revealed marked edema of the corium with vascular congestion and small hemorrhages. About some of the vessels there was cellular infiltration composed entirely of small lymphocytes.

The anatomic diagnosis was agranulocytic sepsis, bilateral bronchopneumonia, submaxillary adenitis, multiple visceral hemorrhages, multiple ulcers of the stomach and colon, cellulitis of the thigh and neck, and atrophy of the bone marrow.

Comment—This was a typical case of agranulocytic angina (Schultz's syndrome) except that there was no distinct ulceration of

the oropharyngeal mucous membrane, but there were ulcerative cutaneous lesions of the face and thigh. The extreme reduction of leukocytes to 100 in each cubic millimeter of blood before death is noteworthy. A heretofore unreported phenomenon is the rapid disappearance of transfused leukocytes and of the patient's own leukocytes, so that from 500 just before transfusion they were reduced to 200 three hours after transfusion. Note should be made that in this case there were 2,000 leukocytes a week before the patient became ill.

CASE 3—A woman aged 54, a housewife, came to the Mayo Clinic on May 12, 1930. Her history, before her present illness, was essentially unimportant. In

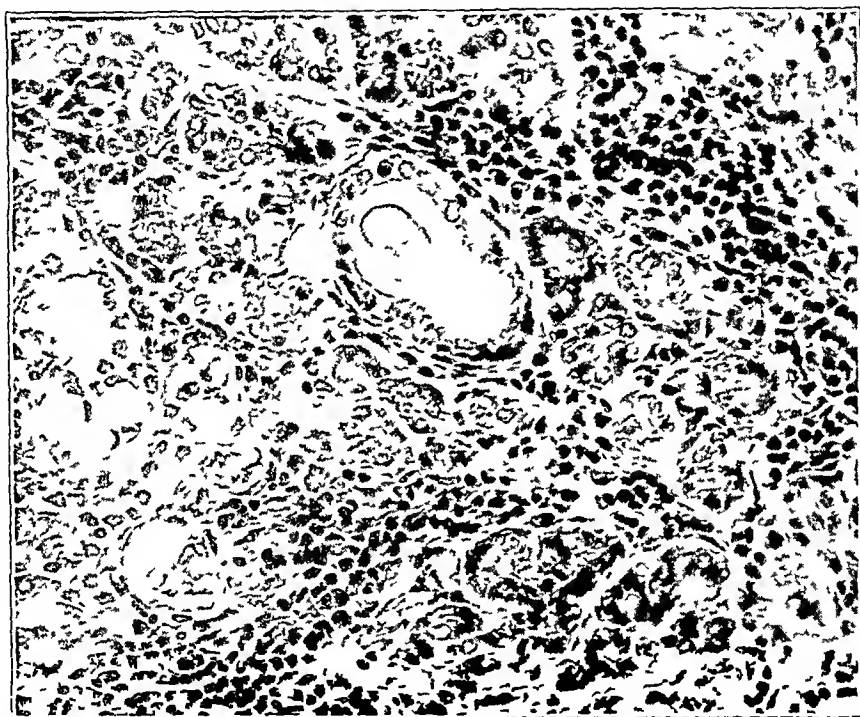


Fig 1—Lymphocytic infiltration mainly in edematous stroma of submaxillary gland and some degeneration of glandular epithelium in a case of agranulocytosis. There is complete absence of polymorphonuclear leukocytic infiltration. Hematoxylin and eosin, $\times 350$.

July, 1929, a sore throat developed. Two weeks later the leukocytes numbered 1,000 in each cubic millimeter of blood, the proportion of polymorphonuclears was 11 per cent. A diagnosis of agranulocytic angina was made by her physicians at home, and the case was reported in detail by Dr. G. Parker,⁹ who saw her in consultation. She was referred to us by Dr. H. W. Brink of Delavan, Ill., for further investigation. At the time of admission she was still easily fatigued and occasionally had a sore throat.

At examination, small hemorrhoids and fibrous tonsils with sealed crypts were found. Examination otherwise gave negative results. Blood counts are given in

⁹ Parker, George. Agranulocytosis with Case Report, *Illinois M. J.* 58:440 (Dec.) 1930.

the table. There were five teeth with periapical infection and two impacted wisdom teeth. A diagnosis of agranulocytic angina was made from the history, although evidence of this disease was not present at the time the patient was under our care. Tonsillectomy was performed without promise of benefit. It was suggested that, if no improvement occurred in a few months, the infected teeth be extracted. The patient's general condition was good at the last report.

Comment—This seems to have been a mild case of agranulocytic angina (Schultz's syndrome), although the neutrophils were never below 11 per cent of the total of 1,000 leukocytes (hypogranulocytosis). Neither the patient nor her family knew of her having suffered, at any time, from ulceration of the throat. What effect the various methods



Fig 2—Ulceration in stomach and necrosis of tissue, and almost complete absence of cellular infiltration in a case of agranulocytosis. Hematoxylin and eosin, $\times 20$.

of treatment had is conjectural. The leukopenia had persisted, to the time of the last report, in spite of removal of evidently infected tonsils. The occurrence of another attack at a later date is to be feared.

CASE 4—A business man, aged 62, entered the Eitel Hospital at Minneapolis on July 22, 1926. In 1916 or 1917 he had had gross hematuria, and in 1919 microscopic hematuria, cystoscopic examination had given negative results. Three weeks before entry he had had gross hematuria, frequency and urgency, general examination gave negative results, and cystoscopic examination disclosed papilloma of the bladder. On July 24, suprapubic cystostomy and cauterization of the tumor were performed by Dr. Gilbert J. Thomas. The day after the operation, fever developed and continued intermittently until sixty-three days after operation. About thirty-three days after the operation sloughing of the operative wound

occurred, and the wound opened. About twenty-four days after the operation, marked ulceration of the mouth and oropharynx developed and included the tonsils and their pillars. The patient's general condition was grave. Examination of the blood on August 6 disclosed that there were 10,700 leukocytes in each cubic millimeter of blood. On August 22, about the time of the beginning of ulceration, the leukocytes numbered 3,600 and on August 23, 3,100, on August 24, the percentage of polymorphonuclears was 4 and of lymphocytes, 96. Further blood counts are given in the table. For several days it was impossible to find a polymorphonuclear, but on August 26 they again appeared, and in two days their percentage again was normal. From September 13 to September 22, the number of leukocytes again was slightly diminished at times and the percentage of polymorphonuclears varied from 47 to 56, but there was no recurrence of symptoms. The patient made a good recovery, and recurrence has not taken place.

Comment—This case fits well into the group of cases of agranulocytic angina (Schultz's syndrome), although the condition appeared after operation. The recovery after complete disappearance of polymorphonuclears for four days is unusual. Whether the operation or the anesthetic had anything to do with the production of the agranulocytosis is conjectural.

CASE 5—A housewife, aged 51, came to the Mayo Clinic on May 19, 1930, and because of abdominal pain and a roentgenologic diagnosis of diaphragmatic hernia she underwent operation on June 21, 1930. Convalescence was uneventful. Leukocytes had numbered 8,700 in each cubic millimeter of blood, May 19, 1930, 9,600, June 25, and 8,500, July 2. The patient returned to the clinic on December 23. She had been well until one week previously, when the following conditions had developed: headache, abdominal soreness with flatulence, and sore mouth and throat which had been different from any previous attack, and which had been associated with aphthous ulcers. She evidently had had fever for several days before admission, and the sore throat had become worse.

At examination, the temperature was 101.8 F, but except for this, aphthous stomatitis was the only significant condition found. Leukocytes numbered 2,500 and erythrocytes 4,260,000 in each cubic millimeter of blood. The concentration of hemoglobin was 13.1 Gm in each 100 cc of blood (normal concentration, from 15 to 17 Gm). On the following day, December 24, leukocytes numbered 1,400, the percentage of neutrophils was 2, of lymphocytes, 84, and of monocytes, 14. Platelets numbered 118,000 in each cubic millimeter of blood. The patient was hospitalized December 26, at which time her temperature was 100 F, and leukocytes numbered 6,000, of which 51 per cent were polymorphonuclears. December 27, the temperature was normal, leukocytes numbered 3,400, of which 45 per cent were neutrophils. A blood culture was negative, and a culture made from a throat swab disclosed green-producing streptococci. There was a gradual rise in the number of leukocytes and in the percentage of neutrophils, until, at the time of dismissal of the patient, January 3, leukocytes numbered 7,600, and the percentage of neutrophils was 67, of monocytes, 3, of lymphocytes, 30, and of reticulated cells, 14. Platelets numbered 136,000 in each cubic millimeter of blood. The smears appeared to be practically normal. The stomatitis had improved markedly, and the patient's general strength was much increased. A diagnosis of mild agranulocytic angina, with spontaneous recovery, was made. No treatment of any kind was administered.

The patient went home on Jan 3, 1931, and returned on January 15. She had been feeling well. On January 13, leukocytes had numbered 3,560, and on January 14, 2,930. The patient returned at her physician's advice, feeling perfectly well. She had not had sore throat or sores elsewhere, and only a few ulcers of aphthous stomatitis. At examination ulcers were not seen. On January 15, the concentration of hemoglobin was 75 per cent, and erythrocytes numbered 4,840,000 and leukocytes, 1,400, in each cubic millimeter of blood. The percentage of lymphocytes was 76.5, of large mononuclears, 11, of neutrophils, 11, and of basophils, 1. Platelets numbered 172,000. No enlargement of glands or nodes was found, and the spleen was not palpable. The patient was given roentgen treatment over the upper end of each femur and humerus and in both cubital spaces, on the basis of results obtained by Friedemann and Elkeles¹⁰. A blood culture was again negative, and a culture made from throat swabs contained green-producing streptococci, gram-positive bacilli and staphylococci. Four days later a moderate number of small ulcers was present, they appeared much like those of aphthous stomatitis. At the time the ulcers appeared, leukocytes numbered 5,300, the percentage of lymphocytes was 67, of large mononuclears, 13, and of neutrophils, 30. The ulceration gradually spread to the anterior pillars and involved the tonsillar region. There was slight swelling in the cervical region and some tenderness. The ulcers gradually improved, and by January 26 were almost completely healed. The leukocyte count continued to be high, compared to what it had been. No cause could be found for this increase in the number of leukocytes except possibly the stimulation of the bone marrow by the roentgen rays. The patient has been under observation until the time of the writing of this report and has not shown evidence of recurrence of the condition.

Comment—Apparently this is a case of agranulocytic angina (Schultz's syndrome), the second attack was especially characteristic. The ulceration, although definite, was not marked. The rapid recovery from the first attack, with the early relapse, and recovery from the second attack are noteworthy. It may be possible that the recovery can be attributed to the roentgen treatment, given according to the method of Friedemann, with the use of 1/20 erythema dose. The increase in the number of leukocytes following its use is worthy of note.

CASE 6—A housewife, aged 48, first came to the Mayo Clinic on Aug 19, 1921, she returned seven times in the ensuing nine years. Leukocytes in 1921 and 1922 were normal in number.

Subtotal abdominal hysterectomy was performed on Nov 4, 1930, for fibromyomas. Recovery was uneventful for ten days. Then slight, apparently superficial, pain developed in the left side of the thorax, and slight tenderness in the pelvis. General examination of the thorax gave negative results. Evidence of phlebitis was not found. Seventeen days after operation slight pain developed on the inner surface of the right thigh, which gradually became worse and involved the whole thigh. There was deep-seated tenderness but no edema. A diagnosis of phlebitis was made, the leg was elevated and heat was applied. Leukocytes, ten days after operation, numbered 18,800 in each cubic millimeter of blood. On

10 Friedemann, U, and Elkeles, A. Die Roentgenbehandlung der Agranulocytose, Deutsche med Wchnschr 56 947 (June 6) 1930.

December 11, thirty-seven days after operation, sore throat and a temperature of 103 F developed. On December 12, leukocytes numbered 4,600. On December 15, the number of leukocytes had fallen to 2,000, of which none was a polymorphonuclear, erythrocytes numbered 4,580,000, and the concentration of hemoglobin was 65 per cent. Further blood counts are given in the table. The temperature continued high until the death of the patient, December 21. The patient was extremely weak, but her appearance was not that of extreme illness. Two blood cultures, a Widal test and an agglutination test for undulant fever gave negative results. Typhoid bacilli were not found in the stools. There was a moderate amount of albumin in the urine, and the roentgenogram of the thorax did not disclose any abnormality. The patient's course was rapidly downward. Large doses of yellow bone marrow were given without effect, and one transfusion caused a severe reaction. Roentgen treatment was given over both shoulder girdles and over the cervical region, without effect. Death occurred on December 21. Records of necropsy are not available.

Comment—This case should probably be classified with those of agranulocytic angina, although soreness of the throat was not marked and there was no definite ulceration. Agranulocytosis was complete for five days before death. Leukocytes numbered 18,800 in each cubic millimeter of blood a month before the appearance of the agranulocytosis. This suggests either that the depression of the bone marrow resulting in the agranulocytosis was a sequel of the infection, which was accompanied by leukocytosis, that it was the result of the infection causing the sore throat, or that it was the result of some unknown factor that depressed the bone marrow in the interval between the two infections. A rapidly fatal outcome a short time after a patient has seemed relatively well has been noticed by others.

CASE 7—A woman, aged 30, was admitted to the hospital in Waterloo, Iowa, on March 10, 1929. She had been ill one week with a condition of the throat that was thought to be Vincent's angina. There was considerable ulceration in the tonsillar region and adjacent structures. Prostration was fairly marked, the temperature was 102 F, the pulse rate was 120 beats each minute, and respirations were 20 each minute. Examination did not reveal any abnormality except ulceration and redness in the throat. The concentration of hemoglobin was 85 per cent, erythrocytes numbered 4,250,000 and leukocytes 6,700 in each cubic millimeter of blood. The percentage of lymphocytes was 90, of large mononuclears, 9, and of polymorphonuclears, 1. Smears from the throat contained Vincent's organisms. The following day the patient was irrational, her temperature was 104.4 F, leukocytes numbered 6,100, and polymorphonuclears were absent. Further blood counts are given in the table. The next day the gums and mouth were painful, swollen and bleeding, and the swelling extended to the sides of the neck. The patient gradually grew worse, two transfusions of blood were given, and diphtheria antitoxin was administered. Nine days after admission the patient seemed better, the number of leukocytes had risen to 3,950, and the proportion of polymorphonuclears was 76 per cent. Eleven days after admission the patient's condition suddenly became worse and she died soon thereafter. At the time of her death the leukocytes numbered 7,600 and the proportion of polymorphonuclears was 86 per cent.

Comment—From the description, this case seems to have been one of agranulocytic angina. The rather sudden death in the presence of normal values for the total number of leukocytes and a high percentage of granulocytes, even though these were somewhat immature, seems likely to have occurred as a result of some complication.

CASE 8—A girl, aged 4 years, whose family history was unimportant, was brought to the Mayo Clinic on Dec 29, 1929. Her health had been good until the onset of the illness for which she was brought to the clinic. In July she had become pale and listless, and in the six weeks preceding our examination, weakness and anorexia had been marked. There had been some vomiting, dark stools, mild abdominal pain and possibly fever.

At examination, pallor was marked, there was a systolic murmur over the whole precordium, the pulse was moderately accelerated, the spleen and liver were not palpable. The concentration of hemoglobin was 10 per cent, erythrocytes numbered 860,000 and leukocytes 4,000 in each cubic millimeter of blood. The proportion of lymphocytes was 76 per cent, and of neutrophils, 18 per cent. Additional blood counts are given in the table. The Wassermann reaction of the blood, examination of stools and roentgenologic examination of the stomach, colon and thorax gave negative results. Emergency transfusions of blood were given at entry, and many were given later. The second day the tonsils were swollen and red, there was some exudate on the surface and oral fetor was noted. The cervical and left axillary nodes were moderately enlarged, and by rectum a small, smooth mass to the left of the median line was felt. Cultures made from the tonsils did not contain *Corynebacterium diphtheriae*, but many fusiform organisms and spirilla were found. Two blood cultures gave negative results, but *Escherichia coli* was found in the urine repeatedly. On Jan 13, 1930, a small dose of radium was applied to the left submaxillary region. The cervical adenopathy was greatly reduced, and the throat and mouth were practically clear. Several furuncles appeared on the neck, and the symptoms referable to the throat recurred. The temperature continued to be elevated, and bilateral otitis media developed. The inguinal adenitis and the furunculosis in the sternal region progressed to formation of abscess. Cellulitis developed in the region of the left side of the jaw. A cervical abscess was drained surgically. The inguinal adenitis became suppurative, and the abscesses were drained. On February 19, acute tonsillitis with cervical adenitis again developed, and was more marked on the right. On February 21, there was a membranous exudate involving a large portion of both tonsils, and two days later, superficial ulceration. A culture contained Vincent's organisms. Leukocytes numbered 1,000 in each cubic millimeter of blood, of which the percentage of lymphocytes was 84, and of polymorphonuclears, 14. The smears did not, at any time, contain immature leukocytes suggestive of acute leukemia. The ulceration spread widely. Jaundice and cyanosis rapidly developed and continued until the death of the patient, Feb 24, 1930. The patient's temperature varied from 99 to 106 F while she was in the hospital. A diagnosis of agranulocytic angina (hypogranulocytosis) seemed more justified than others. Fetal liver, 1 drachm (3.91 Gm) daily, was given during most of the period of hospitalization.

At necropsy, the distal third of the appendix was reddish purple, it was coiled, moderately distended and covered with a yellowish, fibrinous exudate. A number of ileocecal lymph nodes were enlarged.

There were numerous petechial hemorrhages scattered diffusely in the subepicardial tissue. A minute vegetation, apparently of recent origin, was present

on one of the cusps of the mitral valve. There were numerous subpleural petechial hemorrhages scattered over the surfaces of both lungs, and over the anterior surface of the right upper lobe was an area of subpleural hemorrhage, measuring 1 cm in diameter.

The superior surface of the tip of the tongue was discolored, due to hemorrhage, and there was an area of ulceration, measuring 4 mm in diameter, which was covered with yellowish exudate. A similar exudate also covered the base of the tongue, about the circumvallate papillae. The faucial tonsils were moderately enlarged and deeply hemorrhagic. Over the epithelial surface of the tonsils, dipping into their crypts, was a yellowish, fibrinous exudate. In the crypts the exudate was intimately attached, whereas on the surface of the mucous membrane it could be easily peeled off. There was considerable necrosis of the superficial layers of tissue, and in places the necrosis extended deeply into the tonsils. The pharynx was deeply hemorrhagic and was covered by an exudate similar to that present on the tonsils; there were beginning sloughing and ulceration of the mucosa. The epiglottis was mildly congested. The rima glottidis was edematous, the edema effecting nearly complete closure. The upper part of the larynx, down to and including the vocal cords, was also markedly edematous and congested, and was covered with yellowish exudate such as was present in the pharynx. The mucosa of the vocal cords presented the appearance of superficial ulceration.

The gastro-intestinal tract appeared normal except for the presence of three punched-out ulcers 0.5 cm in diameter in the terminal portion of the ileum.

The mucous membrane of the urinary bladder was edematous, and there were numerous small hemorrhagic areas in the submucosa. The thymus appeared to have undergone complete involution. The diaphyseal marrow of the femur presented a reddish appearance.

Smears from the tonsils, made after death, revealed *Neisseria catarrhalis* (*Micrococcus catarrhalis*), streptococci, *Borrelia vincenti* and *Fusiformis dentium* (Vincent's organisms). Cultures made under the same circumstances, from the contents of the appendix, contained streptococci of a hemolyzing strain, in long chains, and *Escherichia coli*. Cultures from the serosa of the appendix contained *Staphylococcus aureus* in pure culture, and those from the bone marrow of the right femur contained a hemolyzing strain of streptococci in long chains.

Sections of the tonsils and of the pharynx presented extensive regions of ulceration and necrosis (figs 3, 4, 5 and 6). The necrotic tissue remained attached to the base of the ulcer, it was matted together by dense masses of fibrin in which there were clumps of deeply blue-staining material of varying size, probably bacteria. There was extensive thrombosis of the smaller blood vessels. In the pharynx the ulcer extended for a variable depth, in places reaching the muscular layer. In the tonsils the necrosis was most marked about the crypts, and extended as deeply as the fibrous capsule, even traversing it in places. The cellular reaction about the necrotic tissue was very feeble and was composed mainly of small and large lymphocytes and scattered endothelial leukocytes. The polymorphonuclear leukocytes were extremely scanty. There were areas of ulceration of the mucosa of the tongue in the midst of an area of widespread necrosis. The epithelium, in places, remained attached to the underlying tissue, although almost all of it was necrotic. The necrosis extended deeply into the muscular tissue, but the necrotic tissue showed no tendency to separate from its base. There was practically no cellular reaction about the region of necrosis. There was edema of the mucous membrane of the epiglottis and small, focal areas of necrosis, surrounded by infiltration of small and large lymphocytes and immature fibroblasts.

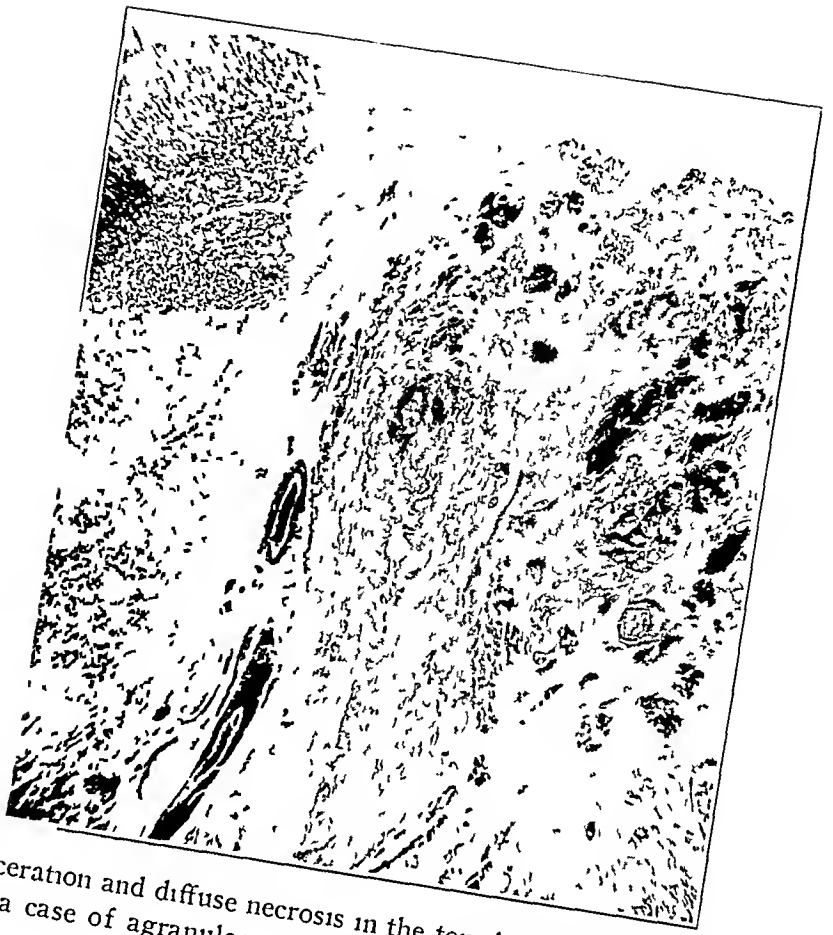


Fig 3—Ulceration and diffuse necrosis in the tonsil, with the presence of clumps of bacteria, in a case of agranulocytic angina Hematoxylin and eosin, $\times 20$

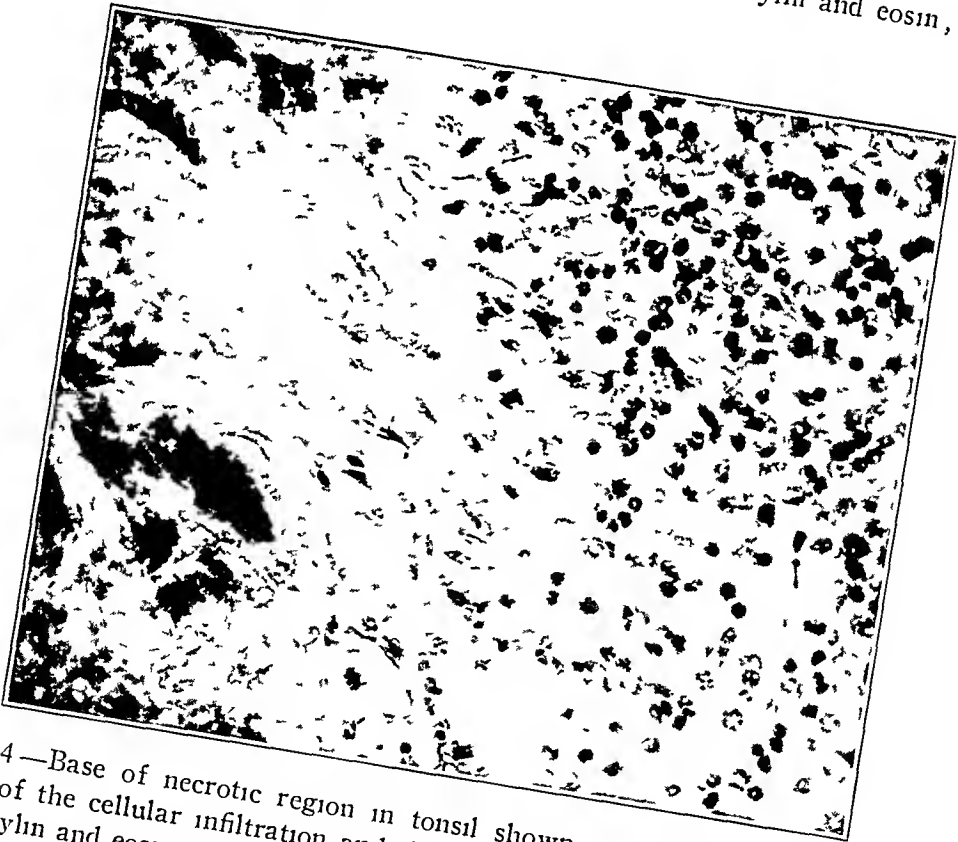


Fig 4—Base of necrotic region in tonsil shown in figure 3, to indicate the sparsity of the cellular infiltration and the marked predominance of lymphocytes Hematoxylin and eosin, $\times 350$



Fig 5—Ulceration of pharyngeal mucosa and necrosis of pharyngeal wall with the presence of clumps of bacteria in a case of agranulocytosis Hematoxylin and eosin, $\times 20$

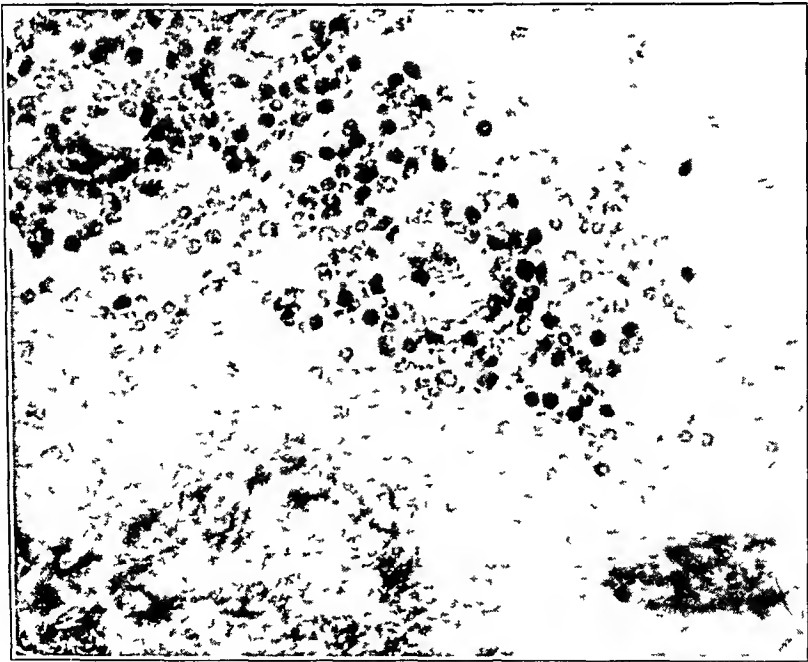


Fig 6—Base of pharyngeal ulcer, showing very sparse cellular infiltration composed almost entirely of lymphocytes and an occasional polymorphonuclear leukocyte Hematoxylin and eosin, $\times 350$

In the bone marrow of the diaphysis of the femur were a small number of cells, and the prominence of the reticulum was increased (fig 7). There were many megaloblasts and occasional normoblasts. Cells of the myelocyte series were hardly to be seen, although here and there an occasional eosinophilic or neutrophilic polymorphonuclear cell could be found. There were, in addition, some large and some small lymphocytes, and an occasional megakaryocyte. Macrophage cells containing phagocytosed blood pigment were numerous. The hepatic parenchyma presented diffuse granular degeneration and a focal region of necrosis about which there was no cellular reaction. There was a deep ulcer in the ileum, filled with necrotic tissue, fibrin and large clumps of bacteria, but there was no

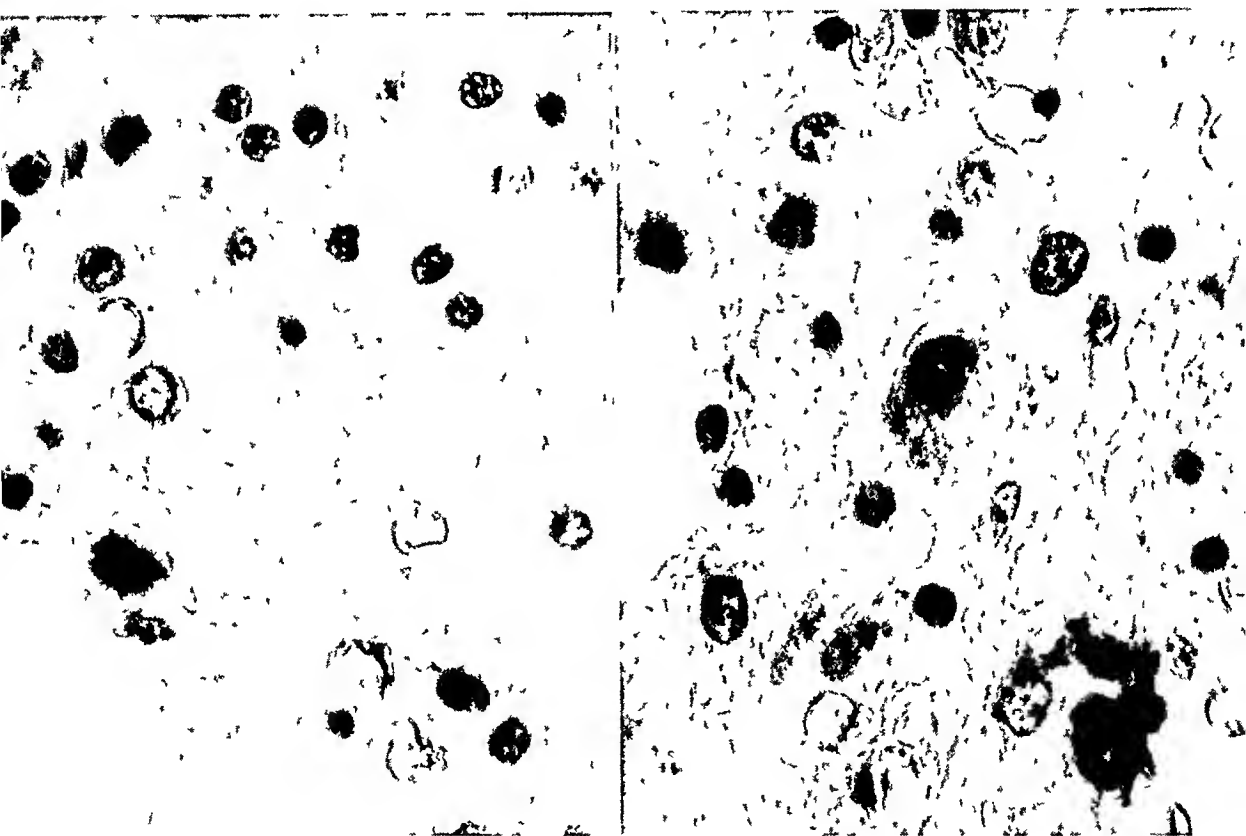


Fig 7—Bone marrow in a case of agranulocytic angina showing prominence of cells of reticulum, small and large lymphocytes and endothelial leukocytes (macrophage cells). Granular cells of myeloid series are absent. Hematoxylin and eosin, $\times 900$.

cellular reaction about this region of ulceration (fig 8). The appendix presented large regions of necrosis, containing large clumps of bacteria, there was some infiltration with lymphocytes about these regions, but there were practically no polymorphonuclear cells. The microscopic study of the other tissues revealed nothing notable pathologically.

The anatomic diagnosis was agranulocytic angina, acute laryngitis with edema of the glottis, acute appendicitis, superficial ulceration of the terminal portion of the ileum, focal necrosis of the liver, petechial hemorrhages of the pleurae, heart and urinary bladder, and involution of the thymus.

Comment—The notable features in this case were the marked anemia and the hypogranulocytosis. The anemia was not of the aplastic type, as shown by the normal or increased percentage of reticulocytes and the fairly normal platelet level. Otherwise, the case would correspond fairly well with agranulocytic angina. Administration of fetal liver apparently had no effect. The presence in the bone marrow of streptococci of a hemolyzing strain, found at necropsy, is of interest.

CASE 9—A housewife, aged 47, came to the Mayo Clinic on July 25, 1929. The family history was unimportant. She had had influenza, scarlet fever and diphtheria. In February, 1929, cold in the head and "grip" had developed, and she had been in



Fig 8—Ulceration and necrosis in superficial layers of the ileum, and absence of cellular infiltration in a case of agranulocytic angina. Hematoxylin and eosin, $\times 100$.

bed one week. She had continued to be weak, some soreness of the throat had developed again, and she had been in bed nine weeks. Beginning in April she had had some fever, had continued to be weak, had received some treatment of the accessory nasal sinuses and had been given a diet high in calories. Leukocytes had numbered 2,750 in each cubic millimeter of blood, of which 83 per cent were lymphocytes and 17 per cent polymorphonuclears. The Widal test and blood cultures had given negative results. The patient had become progressively weaker, had vomited in the week just before her admission to the hospital and had had a slight cough and a slightly sore throat.

At examination the temperature was 99.6 F, and the pharynx was red. General examination otherwise gave negative results. The concentration of hemoglobin

was 61 per cent, erythrocytes numbered 4,510,000 and leukocytes 2,300. The percentage of lymphocytes was 76, and of neutrophils, 11. There was only an occasional polymorphonuclear in the blood smears. The Wassermann reaction of the blood was negative, and achlorhydria was present. Roentgenograms of the thorax, stomach and duodenum gave negative results. There were six infected teeth, and the tonsils had been cleanly removed. The diagnosis was probable mild agranulocytic angina (hypogranulocytosis). The patient was treated with an extract of yellow bone marrow prepared from long bones. Subsequent blood counts made by her physician at home are given in the table. Her physician reported that she is now in excellent condition.

Comment—This case probably was one of mild agranulocytic angina (Schultz's syndrome) with hypogranulocytosis only. At one time, examination of the blood smears disclosed almost no polymorphonuclears, although the lowest number recorded was 11 per cent of 2,300 leukocytes (hypogranulocytosis). The apparent recovery with the use of an extract of bone marrow is worthy of note, although its occurrence may be only coincidental.

CASE 10—A housewife, aged 31, came to the Mayo Clinic on July 21, 1930. She had had good health until March, 1930, when she had had a sore throat, with swelling of the neck and dysphagia, lasting four or five days. The gums had become spongy and sore and had bled somewhat, local treatment had resulted in improvement. She had felt well until May, and the soreness had disappeared. In the two weeks previous to her registration at the clinic she had had a sore throat again and also herpetic lesions on the lips. There had been a small ulcer on the tongue, which had been greatly swollen. There had been soreness of the right cheek and swelling of the right side of the face, which had persisted to the time of her entry. There had been a small blister in the right axilla in the week previous to registration.

At examination there was indurated swelling of the right parotid and submaxillary glands, and of the right side of the neck, and there was some ulceration of the right cheek. There were superficial ulcerations in various portions of the mouth which suggested Vincent's angina, and a smear from the throat contained *Borrelia vincenti* and *Fusiformis dentium*. The concentration of hemoglobin was 60 per cent, erythrocytes numbered 3,860,000, and leukocytes 4,500. The percentage of small lymphocytes was 42, of lymphocytes, 20, of transitionals, 15, of neutrophils, 22, and of eosinophils, 1. Additional blood counts are given in the table. The patient was given 3 grains (0.195 Gm.) three times daily of yellow bone marrow extract and 20 grains (1.3 Gm.) three times daily of ferric citrate. There was gradual improvement, the inflammatory mass disappeared and the ulcers healed. The diagnosis was probable agranulocytic angina, and the possibility of recurrence was explained to the patient. She was dismissed August 16 in fair condition.

Comment—There were apparently two separate attacks. This case is of doubtful diagnosis as the total number of lymphocytes was actually increased at times. Sometimes the blood picture was that of lymphocytosis, at other times that of hypogranulocytosis. Nevertheless, it is somewhat likely that the condition in this case is closely related to agranulocytic angina (Schultz's syndrome), although the low-

est number of polymorphonuclears was 20 per cent of 4,900 leukocytes (hypogranulocytosis). The improvement during the use of bone marrow may or may not be significant.

CASE 11—A farmer, aged 59, came to the Mayo Clinic on Oct 2, 1929. The family history was unimportant. For five years he had had flatulence after meals which had been worse with certain foods. He had had pain in the right upper abdominal quadrant about twice weekly, and a severe attack three weeks previous to his registration at the clinic, fever and weakness had been present since the last attack. No nausea, vomiting or jaundice had been noted, but there had been marked constipation, a small urinary stream, recent anorexia and nocturia graded 1 the previous year. For four years there had been occasional shooting pain in the

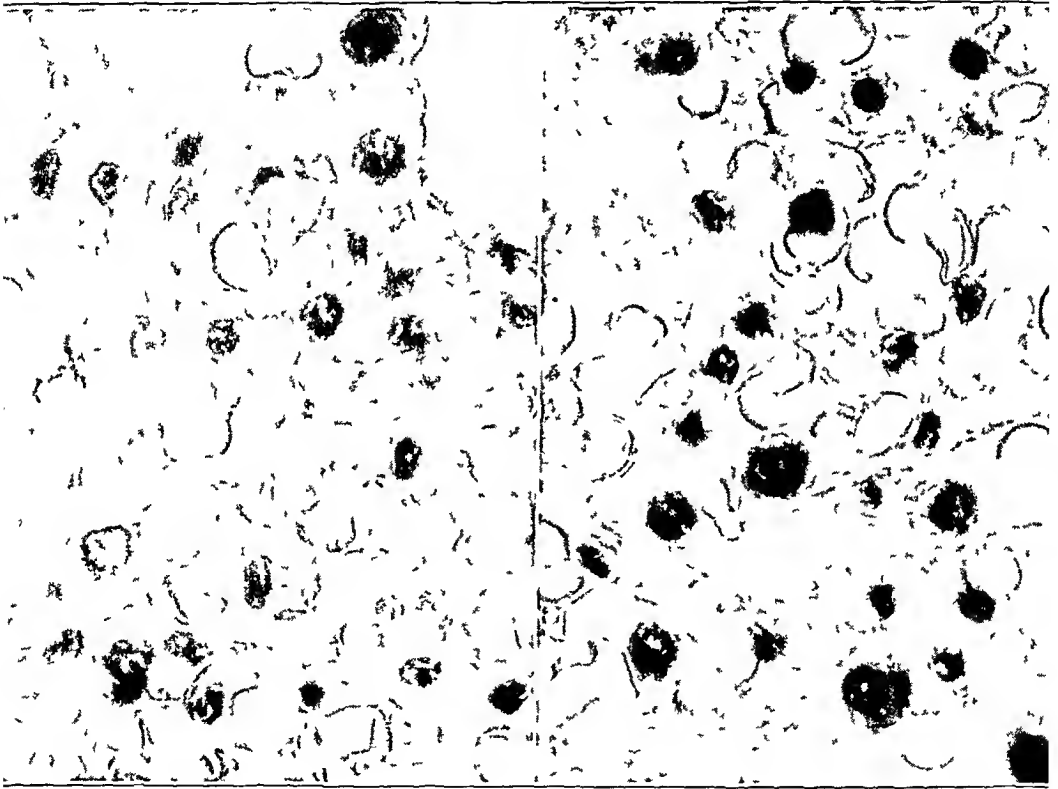


Fig 9—Bone marrow in a case of agranulocytosis, showing numerous plasma cells, lymphocytes and occasional normoblasts. There is almost complete absence of granular leukocytes of the myeloid series. Hematoxylin and eosin, $\times 900$.

left flank, radiating to the groin. The patient's complaint was of weakness, jaundice, fever and abdominal pain.

At examination, the pulse rate was 116 beats each minute, the blood pressure was 112 systolic and 80 diastolic, and the temperature was 102 F. Jaundice graded 2 was present. A mass in the left upper abdominal quadrant apparently was the spleen. The liver was approximately normal to percussion, but the edge was not felt. There was no ulceration of the throat. Albuminuria was graded 2 to 3, the urine contained bile, granular casts graded 1 and an occasional pus cell. Tyrosine was found in the urine twice by chemical examination. The return of phenolsulphonphthalein was 30 per cent, and 225 cc of residual urine was

present. Roentgenograms of the kidneys, ureters and bladder were unsatisfactory, and those of the colon gave negative results. Roentgen examination indicated that the gallbladder was not functioning. The Wassermann reaction of the blood was negative. Examination of stools gave negative results for parasites and blood, but the stools contained bile. The concentration of gastric acids was normal. Three blood cultures contained *Salmonella schottmulleri* (*Bacillus paratyphosus B*). Agglutination tests for undulant fever, typhoid fever and tularemia gave negative results, agglutination tests with *Salmonella schottmulleri* gave positive results in a dilution of 1:2,560. The fragility test disclosed increase in resistance of erythrocytes. The concentration of urea was 38 mg in each 100 cc of blood, and of bilirubin, was variously 4.1, 4.2 and 3.8 mg in each 100 cc of serum. The van den Bergh reaction was direct. The concentration of hemoglobin was 35 per cent, and the erythrocytes numbered 1,960,000 in each cubic millimeter of blood. The number of leukocytes in each cubic millimeter of blood was, successively, 2,200, 1,100, 1,100, 1,200, 1,000, 600, 900, 700, 1,200, 1,000, 1,000, 1,100, 1,000, 3,000, 1,800, 400, 1,600, 1,800, 1,500, 800 and 1,600. Further data are given in the table. The percentage of polymorphonuclear leukocytes was 13 on the day of the patient's admission to the clinic, 56, two weeks later, 64, sixteen days after entry and 20, three days before death. Immature leukocytes were not found, except on one occasion. The diagnosis was *Salmonella schottmulleri* septicemia with agranulocytosis. Six transfusions of 250 cc of blood were given, and 200 mg of acriflavine was given intravenously. The patient gradually became worse, went into a typhoid state and died. Before death, generalized impetiginous eruption developed, especially over both buttocks, and a bullous eruption appeared in the mouth, which somewhat simulated the oral lesions of pemphigus.

At necropsy numerous bluish macules, from 1 to 8 mm in diameter, were found over the skin of the trunk, laterally and posteriorly. There was moderate jaundice.

The epicardial fat was bile-stained, and there were some petechial hemorrhages over the posterior surface of the right ventricle, near the base. The myocardium was somewhat softened, and in the subendocardial tissue there was a faint yellowish mottling, as of fat. There were small, firm, nodular lesions from 1 to 2 cm in diameter, scattered through both lungs, the result of consolidation. The spleen weighed 1,225 Gm, was of normal consistency and presented a diminution in the prominence of the lymphoid follicles. The liver weighed 2,565 Gm, but showed no other significant gross pathologic changes. The esophagus revealed, in its lower portion, many superficial erosions. In the cecum, ascending colon and proximal half of the transverse colon, there were many mucosal abscesses, measuring from 1 to 2 mm in diameter. There was some edema and some hemorrhage involving the mucosa of the bladder. The prostate gland was slightly enlarged. The entire right lobe had been destroyed and was replaced by an abscess. In the left lobe there was an abscess measuring 1 cm in diameter.

Sections of the bone marrow of the shaft of the femur revealed that the cells were sparse and that there was a moderate increase in the amount of fat (fig 9). The most striking feature was the presence of numerous plasma cells, occasional megaloblasts and normoblasts, small and large lymphocytes and large endothelial leukocytes. Polymorphonuclear leukocytes and myelocytes were almost completely absent, only one eosinophilic neutrophil was seen in the entire section. Occasional large mononuclear cells contained mitotic figures.

In the lower lobe of the left lung, thrombosis of some of the veins were seen. There was evidence of organization in thrombi, and surrounding them were regions

of infection. In scattered situations elsewhere the pulmonary alveoli were filled with fibrin and erythrocytes, but leukocytic infiltration was absent in the regions of consolidation. Sections of the right lung presented essentially the same appearance except for the absence of infection. In the rectum, a small region of necrosis beneath the intact mucosa was surrounded by a thin wall of lymphocytic infiltration, but there were no polymorphonuclear leukocytes.

Both kidneys revealed granular degeneration of cells of the tubular epithelium and small lesions of focal necrosis scattered throughout the cortex. These portions were infiltrated with lymphocytes and endothelial leukocytes. The wall of the prostatic abscess was edematous and infiltrated with lymphocytes. Polymorphonuclear leukocytes were entirely absent. Sections of the rectus abdominis muscle revealed small hemorrhages between bundles of muscle fibers and places in which the muscle fibers were swollen, hyaline in appearance, without striations and with completely degenerated nuclei. In the corium of the skin, there were miliary abscesses composed of small and large lymphocytes and a few polymorphonuclear leukocytes.

The anatomic diagnosis was paratyphoid fever, with multiple small ulcers in the colon, agranulocytosis, splenomegalia, hypertrophy of the liver, fatty changes in the myocardium, jaundice with hemorrhagic bullae and abscesses of the skin, bronchopneumonia, acute nephrosis, Zenker's degeneration of the rectus abdominis muscles, and multiple abscesses of the prostate gland.

Comment—This case of hypogranulocytosis does not belong in the group of agranulocytic angina (Schultz's syndrome). It is of special interest because of the continued presence of *Salmonella schottmulleri* in the blood and the positive agglutinative property of the serum in high dilution for this organism. Whether there was an actual case of paratyphoid fever complicated with the prostatic abscess, or whether the prostatic abscess was primary and the septicemia secondary, must remain conjectural. The well marked anemia is also notable. The six transfusions of blood seemed of little value. Acriflavine was not given a fair trial.

CASE 12—A housewife, aged 55, came to the Mayo Clinic on April 14, 1930. The family history was essentially unimportant, and the patient had been healthy previously. Seventeen days before her registration at the clinic she had had so-called influenza, and her nose had been swollen. She had been given cathartics. Hemorrhoids, which she formerly had had, recurred, sloughed and left an anal ulcer. This caused soreness, and a feeling of anal obstruction and tenesmus.

At examination, an open wound was found, which involved the whole posterior portion of the anus. The concentration of hemoglobin was 52 per cent, erythrocytes numbered 3,870,000, and leukocytes 3,600 in each cubic millimeter of blood. A differential count was not made. Treatment of the ulcer and injection into the hemorrhoids was carried out, with good results. Thirteen days after rectal treatment there were general malaise, anorexia, aching in the bones, a temperature of 100 F, indefinite soreness in the left lower abdominal quadrant, headache and constipation. On the patient's readmission to the hospital the temperature was 101.5 F, and it varied from 100 to 104 F until she died. At readmission, leukocytes numbered 350 in each cubic millimeter of blood, of which 51 per cent were lymphocytes and 36 per cent polymorphonuclears. Additional blood counts are given in the table. Attempts at agglutination of *Alcaligenes abortus*, *Eber-*

thella typhi (*Bacillus typhosus*) and *Salmonella paratyphi* (*Bacillus paratyphosus A*) and *Salmonella schottmulleri* (*Bacillus paratyphosus B*) gave negative results. Blood cultures were contaminated. The concentration of bilirubin was 28 mg in each 100 cc of serum, the van den Bergh reaction was direct, the concentration of urea was 30 mg in each 100 cc of blood. Three days after admission there were soreness and a tender mass in the right lower abdominal quadrant. The day before death, ulceration developed on the right buttock, and there was a large hemorrhagic inflammation on the right arm. Operation for the abdominal abscess was not considered advisable. The concentration of urea was 126 mg and that of creatinine, 52 mg in each 100 cc of blood on the day of death. The patient died eight days after she reentered the hospital. Permission for necropsy was refused.

Comment—This patient did not have angina and cannot be considered as having had agranulocytic angina. The leukocytes were very few and the total number of granulocytes very small, although the percentage (35 per cent of 350) was not exceptionally low. There was leukopenia when the patient first entered the clinic, but former records of leukocyte counts were not available. This case illustrates, as does case 8, the possibility of the anus and rectum being the principal sites of the infection. There was moderate anemia.

CASE 13—A contractor, aged 54, came to the Mayo Clinic on July 14, 1930. The family history was not significant. In April, 1930, the patient had become weak and fatigued, and boils had appeared on all parts of the body. His condition gradually had become worse. In the last six weeks before he came to the clinic the left leg and hand had been numb.

At examination, the temperature was 99.2 F, there were slight icterus, many small furuncles, a palpable spleen and liver and a small anal ulcer. The concentration of hemoglobin was 18 per cent, the erythrocytes numbered 1,990,000, leukocytes, 1,000 and platelets, 144,000 in each cubic millimeter of blood. Reticulocytes were present in the proportion of 12 per cent. Additional counts are given in the tabulation. The Wassermann reaction was negative. The first blood culture was negative, but the second contained a streptococcus of a hemolyzing strain. The urine contained occasional erythrocytes and leukocytes. The concentration of bilirubin was 1 mg in each 100 cc of serum, that of urea was variously 32 and 38 mg in each 100 cc of blood, and the value for gastric acids was normal. The temperature ranged from 99.5 to 104.5 F. Treatment consisted of transfusions of blood and one intravenous dose of gentian violet. Death occurred thirteen days after the patient entered the hospital. The diagnosis was septicemia from a hemolyzing strain of streptococci, with hypogranulocytosis.

Comment—This patient did not have angina. The hypogranulocytosis was associated with an infection of the skin and of the anus. There was marked anemia which was not of the aplastic type, as was indicated by the practically normal values for platelets and reticulocytes. The failure of the gentian violet given intravenously, and of the transfusions, to produce cure should be noted. The streptococcic septicemia probably was a secondary event.

CASE 14—A hotel waiter, aged 40, came to the Mayo Clinic on Oct 28, 1929. He had been well until March, 1929, when he had had chills, a temperature of 103 F and urinary frequency. He had been in the hospital nine weeks, when he had had fever, dysuria, urinary frequency and pyuria. An abscess of the right foot had been incised, and pus had drained from it for six weeks. An abscess of the sternal region had been incised twice. Pain had developed in the lumbar portion of the spinal column, had increased and had been aggravated by motion. He had been practically bedfast since the onset of the illness and had lost 75 pounds (34 Kg).

At examination there were a temperature of 99.5 F, slight redness of the throat, ulcerative gingivitis, a palpable spleen, the scar of an abscess on the right foot and a sinus in the sternal region. The concentration of hemoglobin was 63 per cent. The erythrocytes numbered 3,760,000 in each cubic millimeter of blood, and leukocytes, 2,000, 83 per cent of which were lymphocytes, 10 per cent, large mononuclears, and 7 per cent, transitionals, neutrophils were absent. Urinalysis disclosed a few pus cells and a trace of albumin in two specimens. The Wassermann reaction of the blood and blood cultures were negative. Smears and cultures from the mouth disclosed *Fusiformis dentium* and *Borrelia vincenti*, but no *Corynebacterium diphtheriae*. Two smears from the sternal sinus did not contain actinomyces or *Mycobacterium tuberculosis*. Roentgenograms of the thorax suggested that there were foreign bodies in the soft tissues below the left clavicle, those of the thoracic portion of the spinal column indicated that there was an increase in the density of the twelfth thoracic and the first lumbar vertebrae, suggesting metastatic carcinoma, whereas those of the kidneys, ureters and bladder did not give evidence of abnormality. The diagnosis was chronic infection with agranulocytosis, involving the urinary tract, spinal column, sternum and foot particularly. Tuberculosis was also considered. There was gradual failure, and the patient died twenty-three days after admission.

Necropsy revealed a deep ulcer over the right side of the manubrium and over the mesial third of the right clavicle. This ulcer represented the opening of a sinus between the second and third ribs on the right side, and behind the manubrium and the posterior surface of the upper half of the sternum, the tract also connected with a narrow channel that led to the right axilla. Along the latter tract there were several cystlike accumulations of a clear, light brown fluid. The spleen weighed 780 Gm. Its consistency was moderately increased. The lymphoid follicles were prominent. In the descending colon and rectum there were numerous, superficial, discrete, dark pink ulcers, more numerous in the lower part of the rectum. Between the twelfth thoracic and first lumbar vertebrae, an abscess was encountered which involved the intervertebral disk and which was continuous with a large cavity posterior to the right psoas muscle. The abscess contained 20 cc of viscid, purulent material. There was no evidence of involvement of the vertebrae.

Sections of skin in the region of the ulcer presented little evidence of inflammatory reaction, there was practically no cellular infiltration. The sinus tract consisted of a thick layer of granulation tissue, which was infiltrated densely with lymphocytes, plasma cells and endothelial leukocytes, many of which were phagocytic. A part of the fibrocartilage of the intervertebral disk was replaced by fibrous tissue which was densely infiltrated with lymphocytes, plasma cells and many phagocytic cells, and there were numerous newly formed capillaries. The psoas muscle revealed only slight infiltration with lymphocytes and some degeneration of the muscle fibers.

The anatomic diagnosis was chronic spondylitis, with a paravertebral abscess on the left, chronic arthritis of the right sternoclavicular joint, with ulcer of the skin, ulcerative proctitis and sigmoiditis, splenomegalia, and agranulocytosis.

Blood Counts in Fourteen Cases

Case	Date	Time	Cells in Each Cubic Millimeter of Blood			Differential Cell Count of Blood, per Cent							Leukoblasts	Reticulocytes, Percentage of Erythrocytes in Same Fields of Smear	Platelets in Each Cubic Millimeter of Blood, Thousands
			Hemoglobin, per Cent (Dare)*	Erythrocytes, Millions	Leukocytes	Lymphocytes	Neutrophils	Eosinophils	Basophils	Monocytes					
										Large Mono nuclears	Transitionals				
1	11/17/23		75	4 27	12,700	31 0	64 5	1	0 5	1 0	2 0				
	9/27/26		79	4 36	10,000										
	1/ /27		76	4 70											
	2/23/28		68	3 50	3,500										
	2/29/28		77	4 07	6,400										
	3/29/28		60	3 64	1,600										
	3/31/28				1,600	96 0					4 0				
	4/ 1/28				1,700										
	4/ 2/28		55	3 65	1,600	88 0	7 5		0 5	3 0	1 0				
	4/ 3/28				1,100	92 5	4 5		1 0	2 0					
	4/ 6/28				3,600	46 5	46 0			5 0	2 5				
	4/14/28				11,200	25 0	70 5		0 5	2 0	2 0				
	4/16/28				12,400	18 0	77 5		1 5	1 0	2 0				
	4/25/28		73	3 95	6,000										
	6/18/28		76	4 01	2,800	77 0	23 0								
	6/20/28				2,800										
	6/21/28				3,000										
	6/24/28				1,500	98 5	1 5								
	6/30/28†				1,500										
	7/4/28		50	3 46	1,000										
2	3/28/22		64	4 68	7,800										
	12/19/24		70	3 94	7,100										
	12/21/25		59	4 03	7,000										
	1/12/26		56	3 97	7,400	14 0	79 0	1		2 5	3 5				
	12/ 7/26		63	4 09	10,000	21 0	78 5		0 5						
	11/16/28		73	4 11	3,200	100 0									
	11/17/28				2,000										
	11/20/28				1,100	100 0									
	11/22/28	9 30 a m			900										
		12 30 p m			500										
		9 00 p m			200										
	11/23/28	7 30 a m			150										
		11 30 a m	45	3 34	150										
		3 15 p m			125										
	11/24/28	7 30 a m			100										
3	8/ 3/29†		66	3 40	1,000	89 0	11 0								
	5/ 5/30†				2,800										
	5/12/30		81	4 52	3,800	29 0	65 5		1 5	1 0	3 0			135	
	5/13/30				4,500	36 5	60 0		1 5	1 0	1 0				
	5/20/30		81		3,600										
	10/10/30		77†	4 88	2,400	69 0	29 0		1 0	1 0					
	11/20/30		78†	4 60	2,000	53 0	40 0		3 0	4 0					
4	8/ 6/26				10,700										
	8/22/26				3,600										
	8/23/26				3,100										
	8/24/26		72	4 36	2,800	96 0	4 0								
	8/25/26						None					0 8			
	8/26/26		74	4 41	5,400	70 0	30 0							125	
	8/27/26				6,500	40 0	60 0								
	8/28/26				8,300	30 0	70 0								
	8/30/26				9,700	22 0	78 0								
5	11/19/27§				6,600	32 0	65 0	2	1 0						
	5/ 3/28§				6,700	32 0	63 0	3	1 0						
	5/19/30§		16 7		8,700										
			(Gm.)												
	6/25/30§		60	4 17	9,600										
	7/ 2/30§				8,500										
	12/22/30§		13 1	4 26	2,500										
			(Gm.)												
	12/24/30				1,400	84 0	2 0			14 0				118	
	12/26/30				5,700	28 0	46 5			25 5					
	12/27/30				6,800	47 0	51 0			2 0					
	12/28/30				3,400	50 0	45 0			5 0					
	12/29/30				4,200	39 0	55 0			6 0					

Blood Counts in Fourteen Cases—Continued

Case	Date	Time	Hemoglobin, per Cent (Dare)* (Gm)	Cells in Each Cubic Millimeter of Blood		Differential Cell Count of Blood, per Cent							Reticuloocytes, Percentage of Erythrocytes in Same Fields of Smear	Platelets in Each Cubic Millimeter of Blood, Thousands
				Erythrocytes, Millions	Leukocytes	Lymphocytes	Neutrophils	Eosinophils	Basophils	Monocytes		Leukoblasts		
										Large Mono nuclears	Transitionals			
	12/30/30				7,000	40 0	57 0		1 0	2 0				
	12/31/30		17 2	4 77	5,150	31 5	64 5		1 0	3 0				
	1/ 2/31		76	4 46	5,800	33 0	64 5			2 5				
	1/ 3/31				7,150	30 0	67 0			3 0				
	1/ 7/31		76	4 35	6,400	48 0	51 0							
	1/10/31				6,100	49 0	49 0	1	1 0					
	1/13/31				3,560	85 0	15 0							
	1/14/31				2,930	71 0	27 0				2 0			
	1/15/31		75	4 85	1,400	77 0	11 0		1 0	11 0			172	
	1/16/31	a m			1,800	86 0	2 0		1 0	11 0				
		p m			2,100	71 0	3 0		1 0	25 0				
	1/17/31	a m			2,000	79 0	2 0		2 0	17 0				
		p m			3,100	87 0	4 0		2 0	7 0				
	1/18/31	a m			3,800	87 0	3 0			10 0				
		p m			3,900	83 0	3 0	3		11 0				
	1/19/31	a m	80	4 48	2,900	56 0	26 0			18 0				
		p m			5,300	71 5	9 5		0 5	18 5		1 0		
	1/20/31	a m			5,500	57 0	30 0			13 0				
		p m			5,900	55 0	34 0			11 0				
	1/21/31	a m			7,400	43 0	46 0			11 0				
		p m			10,000	30 0	54 0			15 0		1 0		
	1/22/31	a m			10,200	29 0	52 0			16 0		3 0		
		p m			10,700	27 0	69 0			4 0				
	1/23/31				10,900	27 0	64 0		2 0	7 0				
	1/24/31				11,400	30 0	63 0		2 0	5 0				
	1/25/31				11,600									
	1/26/31				12,000	19 0	75 0			6 0				
	1/27/31				11,400	27 0	70 0		1 0	2 0				
	1/28/31				12,700	28 0	72 0							
6	8/20/21		72		7,700									
	7/ 5/22		70		8,400									
	2/28/27		71	4 59										
	11/14/30				18,800									
	11/17/30				10,600									
	11/22/30				10,200									
	12/12/30				4,600									
	12/13/30		73		6,400									
	12/15/30		65	4 58	2,000	80 0	20 0							
	12/16/30	a m	65	4 39	1,300	95 0	5 0							
		p m			1,500		None							
	12/18/30	a m	55	3 55	1,000		None							
		p m			800									
	12/19/30	a m	55	3 46	800		None						186	
		p m			750									
	12/20/30	a m	50	3 35	800		None						180	
		p m	55	3 71	1,400						0 2	140		
				3 56	1,200		None					154		
	12/21/30		50	3 45	900		None					144		
7	3/11/30			4 24	6,100	94 0				6 0				
	3/12/30			4 26	2,287	100 0								
	3/13/30				1,100	100 0								
	3/14/30				900	100 0								
	3/15/30		85	4 76	950	100 0								
	3/16/30				800	100 0								
	3/17/30				650	100 0								
	3/18/30		4 15		600	100 0								
	3/19/30				3,950	13 0	76 0			11 0				
	3/20/30				9,550	19 0	81 0							
	3/21/30				7,600	14 0	86 0							
S	12/20/29		10	0 86	4,000	76 0	18 0		2 0		4 0			
	12/21/29		15	1 60	4,000	61 0	36 0			3 0		4 5	96	
	12/23/29		38	2 64	3,800	49 0	49 0					3 0	128	
	12/24/29		49	2 92										

Blood Counts in Fourteen Cases—Continued

Case	Date	Time	Cells in Each Cubic Millimeter of Blood			Differential Cell Count of Blood, per Cent						Reticulocytes, Percentage of Erythrocytes in Same Fields of Smear Platelets in Each Cubic Millimeter of Blood, Thousands		
			Hemoglobin, per Cent (Dare)*	Erythrocytes, Millions	Leukocytes	Lymphocytes	Neutrophils	Eosinophils	Basophils	Monocytes				
										Large Mono nuclears	Transitionals			
	12/26/29		52	3 18	4,000	36 0	61 0				3 0			
	12/28/29		58	2 92										
	12/30/29		59	3 39	5,100	54 0	43 0				3 0	2 5	128	
	1/ 2/30		51	3 00	4,000	51 0	46 0				3 0	3 0	96	
	1/ 9/30		40	2 71	2,900	43 0	55 0			2 0				
	1/18/30		38	3 02	2,000	73 0	26 0				1 0			
	1/24/30		50	3 12	2,100	37 0	59 0	1			3 0			
	1/27/30		52	3 13	4,300	20 0	78 0				2 0			
	2/ 6/30		57	3 31	4,800	48 0	48 0	1			2 0			
	2/19/30		58	3 00	4,000	69 0	26 0			3 0	2 0			
	2/20/30		57	3 11	4,100	72 0	25 0				3 0			
	2/23/30		45	2 25	1,000	84 0	14 0				2 0			
	2/24/30		40	2 71	700	86 0	10 0	1			3 0			
9	5/ /29		90	4 61	2,750	83 0	17 0							
	7/26/29¶		80	4 74	2,300	76 0	11 0			3 5	9 5			
					2,700									
	7/29/29		61	4 51	2,300	75 0	8 5			5 5	11 0		242	
					2,700									
	6/20/30					48 5	45 5			1 5	4 5			
	8/28/30		75	4 15	5,300	51 0	47 0				2 0			
	10/13/30#				6,450	48 0	51 0				1 0			
10	7/22/30		60	3 86	4,500	62 0	22 0	1			15 0			
	7/24/30		70	4 09	2,700	39 0	51 5			4 0	5 5	3 3		
	7/25/30		70	4 04	3,900	48 0	44 0			3 0	5 0			
					4,400									
	7/28/30		60	4 28	5,100	73 5	22 5			1 0	3 0			
	7/29/30**		70	4 07	4,900	72 5	20 0		0 5	3 0	4 0			
	7/30/30		70	4 13	4,000	67 0	22 0		1 0	3 0	7 0			
11	10/ 3/29		30	1 77	2,200	84 0	13 0	1		2 0			100	
	10/10/29††		30	2 08	1,000	78 0	21 0				1 0	1 7	80	
	10/19/29		40	2 44	1,000	30 0	64 0			6 0				
	10/27/29				1,800	44 0	56 0							
	10/28/29				1,500	80 0	20 0							
	10/30/29‡‡				1,600									
12	4/15/30		52	3 87	3,600									
	5/ 3/30		60	3 65	350	61 0	36 0		3 0					
	5/ 6/30§§				1,300	41 5	51 5		5 5	1 5			60	
	5/ 7/30				1,300	46 0	47 0		7 0					
	5 /9/30				4,600									
13	7/17/30		20	1 60	850									
	7/18/30		15	1 66	750	94 0	6 0					1 2	82	
	7/23/30		15	1 76	1,000	90 0	4 0		6 0				144	
14	10/29/30		63	3 76	2,000	83 0	None		10 0	7 0				
	10/31/30				3,500	32 0	62 0			6 0				
	11/ 1/30		60	3 76	1,700	65 0	19 0		5 0	11 0				
	11/ 4/30				3,200	56 0	37 0	1		6 0				

* If hemoglobin is reported in grams for each 100 cc of blood, this is indicated

† Smears examined contained practically no granulocytes Differential counts mislaid

‡ Data furnished by Dr George Parker, Peoria, Ill

§ Data furnished by Dr F E Vest and Dr J L Lattimore, Topeka, Kan

|| One immature cell

¶ Fragmentation of nucleus of neutrophils and irregular granulation seen in smears

Smears had normal appearance

** In smears, marked evidence of toxicity in leukocytes, none of immaturity, good distribution of platelets

†† In smears, evidence of toxicity graded 2 in leukocytes, none of immaturity

‡‡ Additional leukocyte counts in text

§§ In smears, evidence of toxicity graded 4 in leukocytes

||| In smears, nothing characteristic

Comment—Although the ulcerative gingivitis might place this case in the category of agranulocytic angina (Schultz's syndrome), it seems much more likely that the infection in the sternal and spinal regions and in the foot was a part of a generalized infection that was consequent on failure of the bone marrow, with its resultant leukopenia, or that the infection caused the leukopenia. The ulcerative gingivitis was probably only a local manifestation of diminished resistance to infection.

SUMMARY OF PATHOLOGIC STUDIES

The characteristic features noted in these cases were marked aplasia of the bone marrow and lack of the cellular reaction that is usually observed about regions of necrosis and infection. In the bone marrow, cells of the myelocytic series were barely to be seen, and proliferation of granular cells appeared to be at a standstill.

The peculiar inflammatory reaction that was observed seemed to be merely a consequence of the absence of circulating granular leukocytes. Tissue necrosis and ulceration, whenever they occurred, presented only the distinguishing feature of being unaccompanied by polymorphonuclear leukocytic infiltration. What cellular reaction did occur was comprised mainly of lymphocytic infiltration and the appearance of endothelial leukocytes (macrophage cells). Observation on the type of pathologic tissue reaction in this condition, namely, the lack of development of the protective inflammatory barrier to infection, suggested clearly the reason for the spread of such infection. It was evident, from complete pathologic studies in such cases, that the most common site for the development of focal regions of infection and necrosis was along various parts of the digestive tract, particularly at those points where bacteria are normally abundant. The involvement of the submaxillary gland in one of our cases might seem also to have been the result of extension of infection from the oral cavity. It is possible that these infections along the digestive tract were effected by the usual bacterial inhabitants which gained the ascendancy as a result of the removal of the protective mechanism partially inherent in the normal function of the polymorphonuclear leukocytes.

The occurrence in the bone marrow of streptococci of hemolyzing strains in one of our cases probably had little bearing on the primary etiology of the disease. It seems more reasonable to accept the interpretation that there was metastatic invasion of the bone marrow through portals of entry established in various parts of the body, as, for example, through unprotected necrotic lesions in the digestive tract.

The pathologic features were essentially identical in so-called "agranulocytic angina" and in agranulocytosis, which, in one of our cases, was associated with paratyphoid fever. It seems most probable

that in one of our cases of agranulocytosis the original paratyphoid infection played a definite etiologic rôle, although one cannot, of course, exclude an associated, or secondary, independent infection which might have supervened to effect the pathologic process in the marrow, it may be that the infection was made possible by primary insufficiency of the bone marrow

GENERAL COMMENT

The symptoms were diverse and the situation of the lesions was various. Seven cases presented a clinical syndrome that corresponded, in most details, with that described by Schultz, and three others probably belong in this group. The symptoms differed according to the character and intensity of the underlying disease, the situation of the principal lesions and the degree of resistance of the patient. Four presented agranulocytosis or hypogranulocytosis associated with infection manifesting itself outside of the throat. All displayed common reduction of the number of leukocytes and partial or complete disappearance of granulocytes.

In five of the fourteen cases there was a high percentage of monocytes (large mononuclears and transitionals) at some time in the course of the disease, and in another case now under observation, but not included in this report, the percentage of monocytes was 38. Three of these five patients recovered and the sixth, with 38 per cent monocytes, has made temporary recovery at least. On the other hand, two of the patients who died had increased percentages of monocytes. It may be that the increased percentage of monocytes indicates a relatively better prognosis than no increase, although a definite relationship cannot be seen in this group.

It is our opinion that the agranulocytosis and hypogranulocytosis probably are peculiar responses, in the bone marrow and the blood, to various mimical factors. No common etiologic factor appears. Blood cultures in five of our cases were negative. *Salmonella paratyphi*, *Klebsiella pneumoniae* (*Friedlander's bacillus*) and a streptococcus of a hemolyzing strain were found in one case each. In four cases, blood cultures were not made and in two there was a contamination. *Fusiformis dentium* and *Borrelia vincenti* were found in the throat in each of three cases, staphylococci, streptococci of a hemolyzing strain and green-producing streptococci were found in one case, and green-producing streptococci, staphylococci and a gram-positive bacillus in another case. In four cases there were no sore throat and no indication for examination of smears or cultures from the throat. In none was there a history of exposure to any of the chemicals or physical agents known to produce agranulocytosis. All presented evidence of an infection to which there seemed to be little resistance.

When the peculiar blood picture here described is found, a careful search for all possible causes should be made. Particular care should be given to the diagnosis of well recognized diseases that are associated with leukopenia and great reduction of granulocytes. Such diseases are aplastic anemia, acute leukemia with low values for leukocytes, pernicious anemia in an aplastic phase and metastasis to the bones producing the so-called myelophthisic anemia. Careful inquiry should be made regarding intoxication from benzene, the use of roentgen rays or radium and the administration of arsenicals, especially those of an arsphenamine group. Particular care should be paid also to cases in which there is marked increase in the proportion of lymphocytes and monocytes, with or without a decrease in the total number of granulocytes, such as occurs in infectious mononucleosis or glandular fever, chronic or acute lymphatic leukemia with low leukocytic values and monocytic leukemia. In cases in which there is hemorrhage, some difficulty undoubtedly may occur in eliminating from the diagnosis the various forms of purpura, especially purpura hemorrhagica. Moreover, acute aplastic anemia with hemorrhage, and acute leukemia with hemorrhage and a low total leukocyte count, must be excluded. Particular attention should be called to the value of the reticulocyte and platelet counts. The prognosis is extremely poor in any condition in which agranulocytosis develops, few patients have recovered if the leukocyte count has fallen below 1,000 in each cubic millimeter of blood.

Treatment has consisted of the administration of leukocytic extract, gentian violet and acriflavine, given intravenously, transfusions, roentgen radiation, extract of bone marrow, and fetal liver. In some cases specific treatment was not administered. The results with various methods of treatment were inconclusive.

SUMMARY AND CONCLUSIONS

Fourteen¹¹ cases are reported in which the outstanding feature was the leukopenia and partial disappearance of the granular leukocytes (hypogranulocytosis) or complete disappearance of them (agranulocytosis). In seven cases agranulocytic angina was definitely present, and in three it was doubtfully present. In the sense in which they are here used, the terms agranulocytosis and hypogranulocytosis do not indicate entities but probably stand for types of reaction of the leukopoietic apparatus to various types of infection or intoxication. Agranulocytosis is of serious prognostic significance. Death occurred in five of the seven cases of agranulocytic angina, in one of the three doubtful cases of agranulocytic angina and in all of the four cases of agranulocytosis or hypogranulocytosis due to other types of disease.

11 Patients in two additional cases not included in this group were under observation in the hospital at the time this report was being written.

CONGESTIVE HEART FAILURE

XII THE RELATION BETWEEN THE THICKNESS OF THE CARDIAC MUSCLE FIBER AND THE OPTIMUM RATE OF THE HEART^{*}

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The harmful effect of tachycardia in patients with cardiac disease is well recognized. A sustained increase in rate is not infrequently an important precipitating cause of a break in compensation. Occasionally one observes symptoms of congestive failure occurring during an attack of paroxysmal auricular tachycardia in a person whose heart is normal in every other respect. Such a case has been reported by Barcroft, Bock and Roughton¹. However, some animals normally have heart rates which are considerably faster than those of patients with paroxysmal tachycardia. Why is a heart rate of 200 per minute likely to be attended by grave symptoms in men while the resting heart rates of guinea-pigs are more than 220²? Again, why is it that the heart beats 600 times per minute in the mouse and 40 per minute in the horse (Clark²)? If the optimum (i.e., the normal) heart rate is different in different species is it the same in enlarged hearts and hearts of normal size in the same species? What determines the optimum heart rate? It has occurred to us that the recovery time might be related to the length of time required for oxygen to diffuse into the fiber and that this might be greater for larger fibers.

The present researches were undertaken in an endeavor to throw light on these and similar questions in the hope that by so doing a better understanding of congestive heart failure might be attained.

METHOD

As a basis for the study of the normal heart rate electrocardiograms were taken on rats, guinea-pigs, rabbits, dogs, sheep and cows. Adult animals were used. At first a series of tracings were taken on a group of animals successively, but it was soon found that pulse rates obtained

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¹ Barcroft, J., Bock, A. V., and Roughton, F. J. *Heart* 9 7, 1921

² Clark, A. J. *Comparative Physiology of the Heart*, New York, the Macmillan Company, 1927, p. 143

in this way were much above the normal resting pulse rates. The factors of excitement, fear and struggling seemed responsible. Consequently, it was deemed wiser to restrict our series and search for individual animals that could be trained to become quiet while the tracings were made. It was necessary to take repeated tracings on several animals of each species in order to get one or two which were quiet and the pulse rates of which seemed relatively basal. In general, we have assumed that the presence of sinus arrhythmia indicated that the pulse rate was at, or nearly at, the truly normal resting level for the particular animal concerned. No narcotics or anesthetics were used. It was necessary to discard at least four fifths of our tracings, but it is felt that a few observations on quiet animals are more indicative of the normal pulse for the species than any number of unselected observations.

In order to determine the length of diastole the T-S intervals were measured. There is some question as to whether this interval corresponds exactly to the duration of mechanical diastole, but it seems justifiable to assume a fair agreement. The film speed and the standardization of the excursion of the string were varied in the different animals in order to obtain records which could be conveniently and accurately measured.

Electrocardiograms were also taken on six infants less than 6 months of age, on six children of from 3 to 6 years and on six children of from 9 to 12 years. Twelve electrocardiograms on normal adults were selected at random from the files. Similarly, electrocardiograms from six patients with cardiac enlargement without congestive failure, and from six patients with cardiac enlargement with congestive failure were selected. Measurements of the T-S interval were made in all instances.

In tabulating the data it was decided to use averages for the different human series and for dogs, sheep and cows, as the subjects of these species were quiet and seemed reasonably calm. However, since the rats, guinea-pigs and rabbits were usually restless, and even after considerable training many of them seemed excited, it was decided to discard all curves for these animals except those showing the slowest heart rates in each species.

Hearts were obtained from six animals of each species. Blocks of left ventricular tissue were cut at a level about half way between the base and the apex of the left ventricle. These were fixed, embedded, cut and then stained with hematoxylin and eosin. From necropsy material already available, six sections each were chosen of hearts of infants, children of from 3 to 6 years, children of from 9 to 12 years and adults. All these subjects had had normal hearts at autopsy. In addition, six sections were examined from the hearts of subjects who had, at autopsy, enlarged hearts without evidence of congestive failure, and six sections

were studied of the hearts of persons dying with clinical and pathologic evidence of congestive failure

Measurements were made with the micrometer of the width of twelve muscle fibers of the left ventricle in each section, all measurements being made through the nucleus in order to be certain that comparable portions of the different cells were being studied. The greatest and the least values were then discarded and the average width of the other ten fibers was designated as the mean fiber thickness.

RESULTS

The Relation Between Fiber Thickness and Heart Rate in Human Subjects of Various Ages—The data are shown in table 1 and charts

TABLE 1—*Cardiac Fiber Thickness, Cardiac Rate and Length of Diastole in Human Subjects*

Condition of Heart	Age Group	Number of Cases Studied	Fiber Thickness, Microns			Pulse Rate per Minute			Length of Diastole, Seconds		
			Thinnest	Thickest	Mean	Fastest	Slowest	Mean	Shortest	Longest	Mean
Normal	Infants, 2 to 5 mo	6	5.65	9.9	6.8	174	140	156	0.17	0.23	0.20
Normal	Young children, 3 to 6 yr	6	9.37	11.7	10.4	135	100	118	0.24	0.36	0.29
Normal	Older children, 9 to 12 yr	6	10.18	12.7	11.3	104	90	96	0.37	0.43	0.41
Normal	Adults	12	14.60	19.8	16.2	100	58	78	0.36	0.79	0.56
Enlarged, no congestive failure	Adults	6	18.80	27.0	24.5	115	60	84	0.30	0.68	0.49
Enlarged, congestive failure (digitalized)	Adults	6	26.50	42.7	31.8	85	60	76	0.43	0.64	0.53

1 and 2. It is evident that in subjects with normal hearts there is a definite inverse relationship between pulse rate and fiber thickness, and a direct proportionality between the length of diastole and fiber thickness. (We do not mean to imply that heart rate is "regulated" by fiber thickness.)

In patients with cardiac enlargement no such relationship exists. Their fibers are much thicker than those of the normal adult, but their heart rates are somewhat faster. (The average heart rate was more in those patients without, than in those with, congestive failure. This difference is probably to be attributed to the fact that the subjects in the latter group were digitalized.)

The Relationship Between Heart Rate and Fiber Thickness in Animals of Different Species—That these two functions are in some way related appears from table 2, in which it can be seen that the animals with the fastest heart rates have the thinnest cardiac fibers and vice versa. In charts 3 and 4 it is shown that the relationship is not a

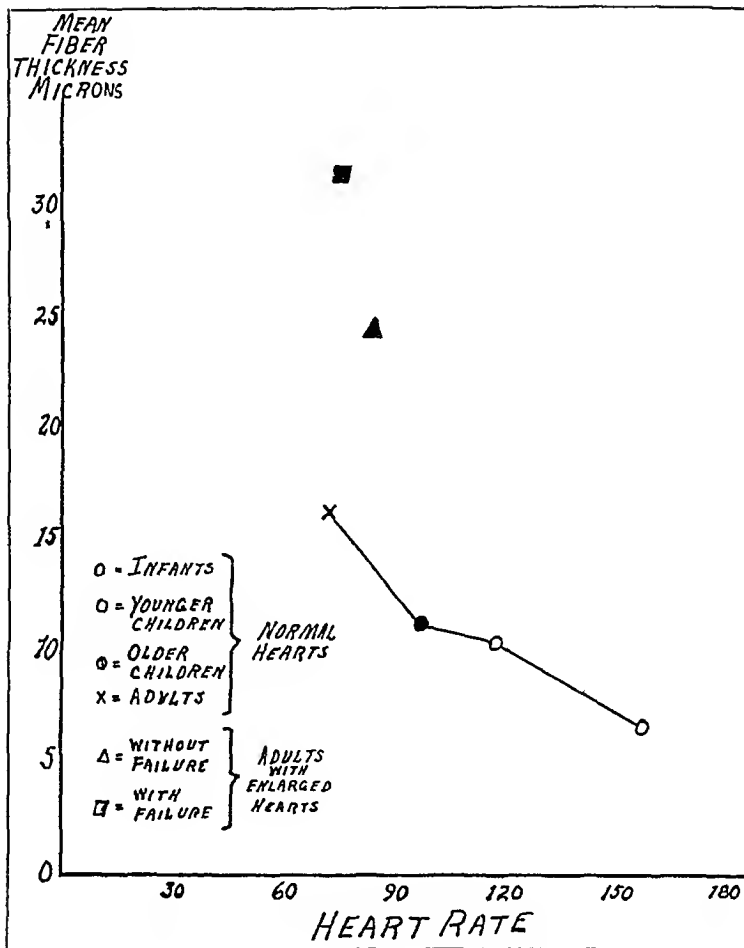


Chart 1—An inverse and more or less linear relationship is shown between the heart rate and the fiber thickness of normal hearts. The values for enlarged hearts do not fall near the line.

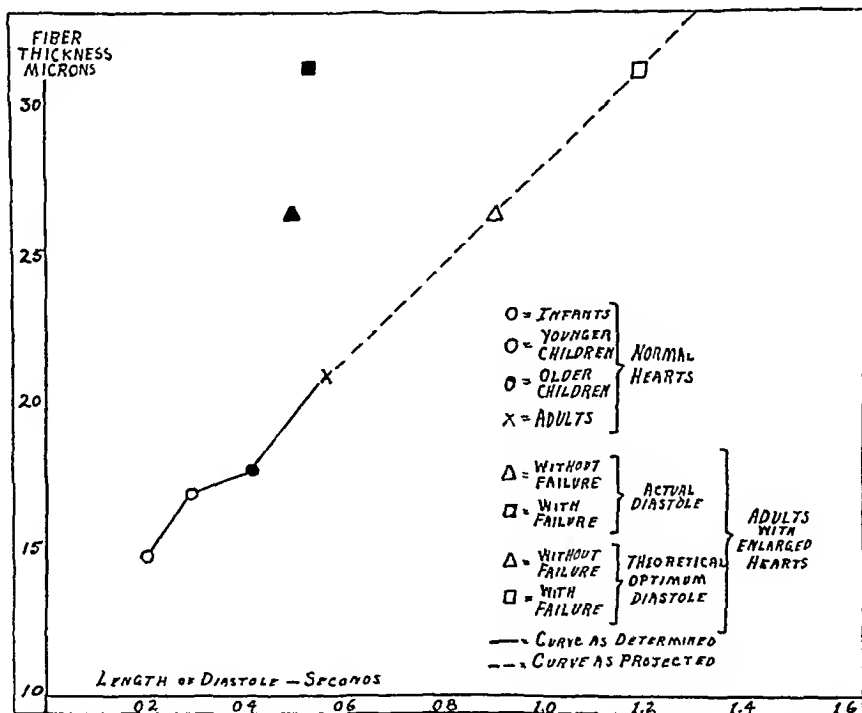


Chart 2—Fiber thickness has been plotted against the length of diastole. The values for normal hearts in subjects of various ages fall reasonably close to a straight line. However, the points for enlarged hearts are not near this line. This seems to indicate that in such hearts the fiber is too thick for the rate, or the rate is too fast for the fiber thickness.

simple linear one but is suggestively logarithmic. In chart 5 the fiber thickness is plotted against the logarithm of the length of diastole, and the curve becomes a line. All the values for the normal animals fall reasonably close to this straight line—certainly as close as could be expected when one considers the numerous possible sources of error in the data. However, the values for enlarged hearts do not fall on the line at all, but are much above it. This is interpreted as meaning that their fibers are much too thick for their heart rates or, conversely, that their heart rates are much faster than optimal for their fiber thickness.

The observations on animal hearts are therefore in qualitative agreement with those on human hearts, and both indicate that a disproportion between heart rate and fiber thickness exists in patients with enlarged

TABLE 2—*Cardiac Fiber Thickness, Cardiac Rate and Length of Diastole in Various Adult Animals*

Species	Number of Animals Studied	Mean Fiber Thickness, Microns	Pulse Rate per Minute	T S Interval, Seconds
Rat	10	11.2	340*	0.10*
Guinea pig	9	12.5	264*	0.15*
Rabbit	9	14.5	141*	0.28*
Sheep	6	14.8	105	0.40
Dog	6	16.8	69	0.56
Man	12	16.2	73	0.56
Cow	6	17.6	60	0.67

* The values given for fiber thickness are averages in all cases. The figures for pulse rates and T S intervals are averages for those animals which remained quiet (man, cow, dog). The other animals usually either struggled or were excited, and the starred values were chosen from those animals which had the slowest pulse rates of their respective species.

hearts. From these data it seems fair to conclude that the optimum heart rate of patients with cardiac disease is considerably less than the optimum rate for normal hearts.

The next question is: How much slower than normal is this optimum rate? Our data furnish no satisfactory answer to the question. The two series of observations, although in qualitative agreement, do not agree quantitatively. The curve obtained from the animal hearts (charts 4 and 5) approaches the logarithmic form, whereas that obtained from the human hearts (chart 2) is nearly linear. When these curves are prolonged so as to reach the degree of fiber thickness of enlarged hearts, the former curve seems to indicate that the optimum rate for enlarged hearts is 10 or less, whereas the prolonged human curve—being linear—points toward an optimum rate nearer 40 for enlarged hearts. These points are illustrated in charts 2 and 5 and in table 3.

In view of this quantitative disagreement, which conclusion is one to believe? We think that the figures derived from the study of the animal hearts are more reliable, for two reasons:

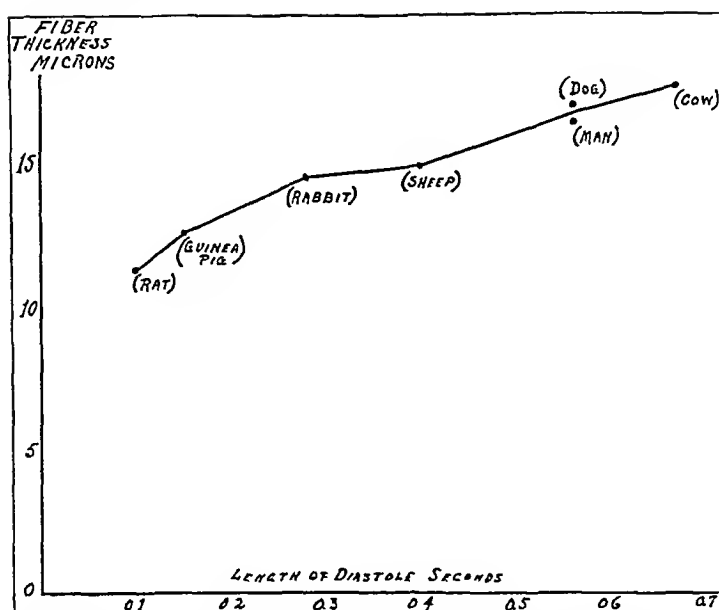


Chart 3—Fiber thickness has been plotted against length of diastole for the normal hearts of the several species. An irregular curve has been obtained.

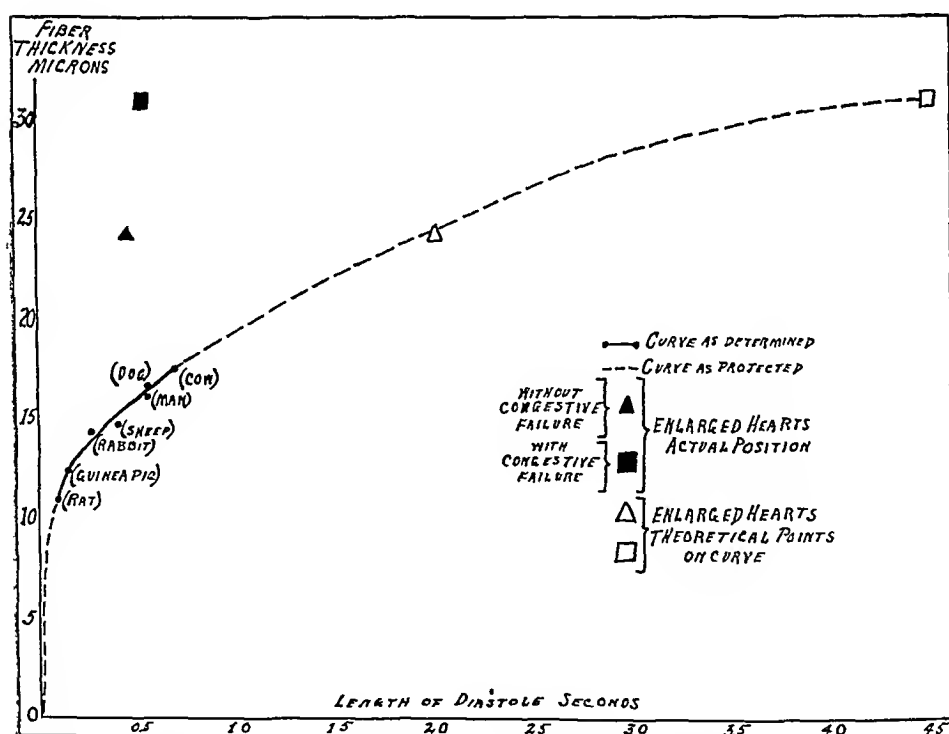


Chart 4—The scale has been changed from that in figure 3. All the values for the normal hearts are fairly close to the curve, but the points for enlarged human hearts are much above it. When the curve is prolonged so as to attain the fiber thickness of the enlarged hearts, a rough estimate of the theoretical optimum length of diastole for such enlarged hearts can be obtained.

In the first place the animal hearts were from adults, and we are attempting to determine the optimum rate for enlarged adult hearts. It is possible that the factor of growth explains the obvious discrepancies between the two sets of data. Thus, the fiber thickness of the infant human hearts was only a little more than one-half that of the adult rat hearts, although the latter animals were less than one-fiftieth as large. Unless this difference is to be attributed to growth we are unable to explain it. In favor of the notion that growth is responsible is the fact that the human fibers are relatively thinner at both the age periods (infancy and 9 to 12 years) when growth is most rapid than at the age (3 to 6 years) when growth is less rapid.

In the second place a logarithmic type of curve, such as was obtained from the study of the animal hearts, is more in accordance with known laws of diffusion of gases. One can consider one half of the muscle

TABLE 3—*The Calculated Optimum Heart Rate for Patients with Cardiac Hypertrophy*

Group	Mean Duration of Systole, Seconds	Calculations from "Animal Curve" (Chart 5)			Calculations from "Human Curve" (Chart 2)		
		Optimum Duration of Diastole, Seconds	Optimum Duration of Cycle, Seconds	Optimum Heart Rate per Minute	Optimum Duration of Diastole, Seconds	Optimum Duration of Cycle, Seconds	Optimum Heart Rate per Minute
Cardiac hypertrophy without congestive failure	0.22	5.89	6.11	10	0.90	1.12	54
Cardiac hypertrophy with congestive failure	0.26	50.2	50.28	1	1.19	1.45	41

fiber as being supplied with oxygen from the capillary on the corresponding side and the opposite half from the capillary on its side. The greatest diffusion distance is therefore one-half the thickness of the fiber, and the mean diffusion distance is one-fourth the thickness of the fiber. If the fiber thickness is doubled, the mean diffusion distance is doubled. However, the mean head of pressure (the oxygen tension in the capillary) is not doubled, but remains the same. As oxygen diffuses, the head of pressure diminishes. Hence, it probably diffuses more rapidly through the outermost than through the central portion of the fiber. Therefore, since the time required for complete recovery to take place after the contraction is dependent on the time required for oxygen to reach all parts of the fiber, one would expect that an increase of twofold in fiber thickness would more than double the recovery period. From such reasoning one arrives at the conclusion that the thicker the muscle fiber the slower the heart rate should be, not only actually but also relatively.

One objection may be raised to this concept, namely, that recovery might take place during systole as well as during diastole. Against this objection one may cite at least three points

(a) If recovery can take place simultaneously with contraction there should be no limit, other than that set by mechanical factors, to the rate at which the heart or any skeletal muscle can contract, and this rate of contraction should be capable of being maintained indefinitely without fatigue. If this is true the normal human heart should be able to beat 250 times a minute for years.

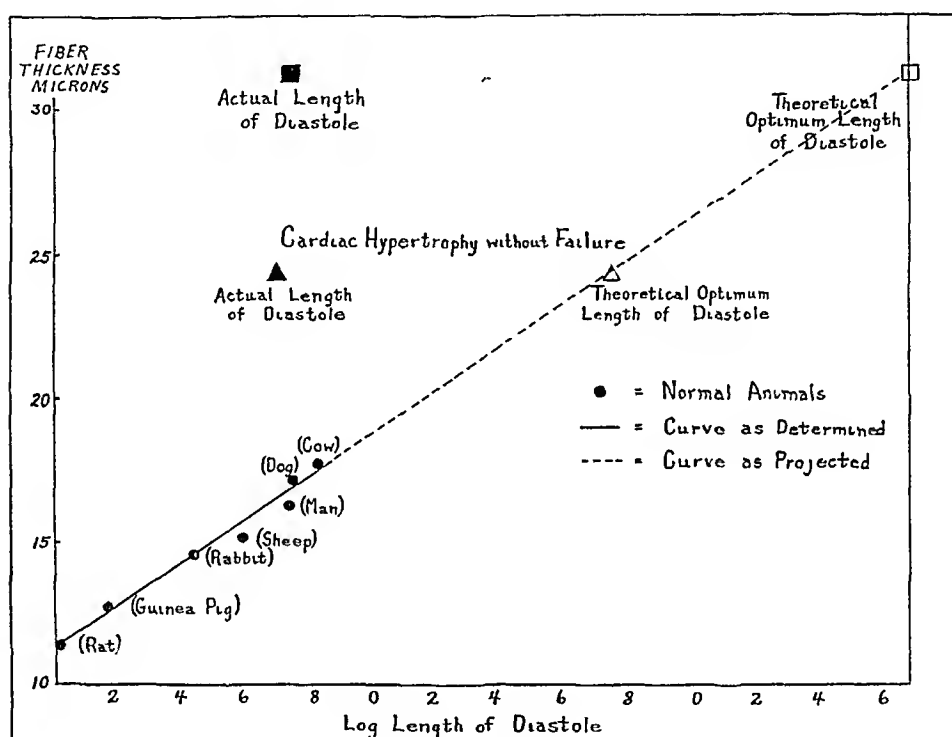


Chart 5—Data on hearts showing hypertrophy with congestive failure. The fiber thickness is plotted against the logarithm of the length of diastole for hearts of the various species. The points so obtained lie very close to a straight line. This seems to indicate a logarithmic relation between fiber thickness and the length of diastole. Such a relationship is in agreement with A. V. Hill's calculations. The actual points for the enlarged hearts do not lie near the optimal normal line, but are much above it. By prolongation of the line, one can see that the optimum heart rate for hypertrophied hearts is apparently very slow.

(b) If recovery, a process which has been demonstrated to consume oxygen and to produce carbon dioxide, can take place during contraction, one ought to be able to demonstrate increased respiration in a muscle during active contraction. Moore³ showed that the carbon dioxide production of tetanized frog's muscle was diminished during

³ Moore, A. R. *J. Gen. Physiol.* 1: 613, 1918-1919.

the contracted state, even though this lasted for as long as thirty minutes. After relaxation a great increase in carbon dioxide production was observed. This experiment cannot be repeated on the heart because it cannot be tetanized, but there is no reason to believe that cardiac muscle differs from skeletal muscle in so fundamental a property.

(c) A. V. Hill⁴ studied diffusion in thin strips of frog muscle suspended in oxygen. According to his calculations a strip of muscle 0.5 mm thick, exposed to oxygen on one side at a temperature of 20°C, would be able to perform one twitch every eight seconds without acquiring an oxygen debt. If, all other conditions being the same, the muscle strip were twice as thick, only one twitch every forty seconds could be performed, whereas if the muscle were one-half as thick one contraction every two seconds would be possible. Hill stressed the importance of the size of the capillary, showing that the "time required for diffusion and recovery varies as the square of the average diameter of the vessels." He also said: "Mr. A. D. Ritchie has pointed out to me that an argument similar to that given here in relation to the size of blood capillaries may be applied to the case of muscle fibers, that is to say, the maximum diameter of a muscle fiber is probably not fixed by mechanical factors but by the speed of diffusion."

For these reasons we conclude that the optimum cardiac rate for patients with cardiac hypertrophy is probably in the neighborhood of 10 or less, the value derived from the study of the animal hearts, rather than about 45, which is the figure arrived at by the study of the human hearts. However, for practical purposes it is not important which figure is correct as both can only be crude approximations and as such a figure would naturally be less for a markedly hypertrophied than for a less enlarged heart. Both sets of observations agree in indicating that patients with cardiac disease, even when at rest and digitalized, still have rates which are much too fast.

The Frequency of Congestive Heart Failure in Patients with Heart Block—If the conclusion which has been drawn—that the rate of the heart in patients with congestive heart failure is much faster than optimal—be correct, one would expect that persons with cardiac disease and abnormally slow heart rates would be less likely to suffer from symptoms of congestive failure than would persons with cardiac disease and normal rates. In order to study the matter, a number of cases of heart block were collected from the literature. No attempt at a complete survey was made.

The data are summarized in table 4. Edes⁵ collected 121 cases of "permanent slow pulse" from the literature. His paper was written

4 Hill, A. V. Proc Roy Soc s B, **104**:39, 1929

5 Edes, T. R. Tr A Am Physicians **16** 521, 1901

before electrocardiograms and polygrams were in general use, and there is some doubt as to whether all of these patients had heart block. However, most of them had pulse rates of 45 or less and many of them had convulsive seizures, so that there can be little doubt that most of Edes's cases showed heart block. In only one of the 121 cases was edema an outspoken symptom, and of the 10 patients with dyspnea at rest, 7 had it only during the convulsive seizures.

The reports by other authors were similar. A positive statement as to the absence of dyspnea and edema was not always made, but it is probably safe to assume that the symptoms would have been mentioned

TABLE 4—*The Frequency of Symptoms of Congestive Heart Failure in Patients with Chronic Heart Block*

Author	Total Number of Cases Reported	Number of Cases in Which Edema Was Reported	Number of Cases in Which Dyspnea at Rest Was Reported	Comment
Edes ⁵	121	1	10	Seven of the ten patients with dyspnea had it only during fainting spells. Diagnosis was not proved instrumentally, but most of the patients probably had heart block.
Mackenzie (Diseases of the Heart, ed 4, New York, Oxford University Press, 1925, p 261)	18	1	1	
Parsonnet and Hyman (Am J M Sc 180 356, 1930)	8	1	1	
Hirschfelder ¹⁰	3	0	0	
Blackhall Morison (The Sensory and Motor Disorders of the Heart, ed 2, New York, William Wood and Company, 1928, p 241)	3	0	0	
Price and Nisse (Am Heart J 5 197, 1929)	2	0	0	Proved cases of heart block.
Ascoli (Ztschr f exper Path u Therap 4 185, 1927)	1	0	0	
Harris ⁸	1	0	0	
Willius ⁹	1	0	0	
Total	158	3	12	

if they were at all prominent. Taking the case reports as given, one finds dyspnea at rest in only about 7 per cent and edema in only about 2 per cent of the cases. When one remembers that chronic heart block is most commonly found in patients with hypertension, arteriosclerosis, rheumatic infection and syphilis, and as a sequel to diphtheria (Butler and Levine ⁶), and if one recalls that all of these diseases except diphtheria are common causes of congestive heart failure, the percentages seem remarkably low. The presence of heart block is proof that the underlying process has involved the heart and, a priori, one would have expected a much higher proportion of patients to have congestive failure, unless heart block in itself tends to protect against this.

⁶ Butler, S., and Levine, S. A. Am Heart J 5 292, 1930

Against this argument certain objections may be raised

(a) Butler and Levine have shown that a fairly large proportion of the cases of chronic heart block are presumably postdiphtheric, and diphtheria rarely causes chronic congestive failure. However, if we assume that diphtheria was the cause of the heart block in one half or even in two thirds of the cases collected in table 4, the percentage of cases with advanced congestive failure (edema) still would remain remarkably low

(b) Dyspnea brought on by exertion is a common symptom in patients with chronic heart block. This is true, but symptoms brought on by exertion are to be attributed to diminished cardiac reserve and are not to be looked on as evidences of congestive failure. In patients with heart block the output per beat is very great even at rest (Lundsgaard⁷) and hence cannot be increased much, and, since their hearts do not accelerate during exercise, their dyspnea is probably due to an inability to increase the circulatory minute volume. Furthermore, many patients with heart block do not have dyspnea even with severe exertion (Harris,⁸ Willius⁹)

(c) Perhaps patients with heart block do not live long enough for congestive failure to develop. On the contrary they often live for remarkably long periods after heart block has become manifest. Hirschfelder¹⁰ reported a case in a patient with heart block of thirty-five years' duration. Mackenzie's and Harris' patients had had it for twenty-nine and twenty-eight years, respectively. None of these three patients had any evidence of congestive failure, all were leading normal lives. Most authors refer to the fact that complete heart block is compatible with long life and good health.

Furthermore, death in patients with heart block is usually sudden, and most frequently occurs during an attack of angina pectoris, or during a fainting spell. The slow agonal death with congestive heart failure is rare in such cases.

(d) Patients may develop heart block and congestive failure simultaneously. This is true, but it occurs only following overwhelming and sudden injury to the heart, such as occurs in certain cases of diphtheritic myocarditis and in patients with coronary occlusion. Such cases are acute and have been purposely omitted from table 4, which includes only cases of chronic heart block.

(e) Perhaps patients with heart block do not have cardiac hypertrophy. On the contrary, most of them do. Mackenzie, for example,

7 Lundsgaard, C. *Deutsches Arch f klin Med* **120** 481, 1916

8 Harris, E. H. *Heart* **14** 289, 1929

9 Willius, F. A. *Ann Clin Med* **3** 129, 1924

10 Hirschfelder, A. D. *Diseases of the Heart and Aorta*, ed 2, Philadelphia, J. B. Lippincott Company, 1913, p 571

made a positive statement concerning the cardiac size in nine of the cases of his series with chronic heart block. In one case no enlargement was noted, in the other cases enlargement of varying degrees was found.

It therefore seems justifiable to conclude that heart block tends, other things being equal, to prevent congestive failure. We believe that the reason for this lies in the fact that such patients have heart rates which approach the optimal rate for hyperthrophied cardiac muscle fibers.

COMMENT

The thesis that congestive cardiac failure, regardless of the underlying etiologic factor, is immediately due to inefficiency (more commonly spoken of as insufficiency) of the cardiac muscle seems to be generally accepted. No one has yet offered an entirely adequate explanation as to why and how the myocardium fails. Attempts to explain the altered function on the bases of structural changes have been unconvincing. It is true that the majority of such hearts do show some fibrosis and some of them exhibit this change to an extreme degree, but in many instances the pathologic changes in the myocardium are altogether inadequate to account for its failure. This point of view has been particularly emphasized by Aschoff and Tawara,¹¹ and more recently by Christian¹² and by Kutschera-Aichbergen,¹³ in whose paper a review of the literature may be found.

If myocardial failure cannot be attributed to myocardial disease, to what can it be attributed? The term "fatigue" has been applied to this gap in our knowledge, but a name is not an explanation. Overwork of the heart, which is usually present in such cases, is undoubtedly a potent factor, but overwork does not explain the progressive nature of the malady in the face of a load which is not increasing and is often diminishing. Progressive valvular or myocardial damage is more often absent than present in a large series of cases. Certain chemical changes in the cardiac muscle have been found, namely, alteration in the phosphatides by Kutschera-Aichbergen,¹³ diminution in phosphates by Laszlo¹⁴ and decreased potassium content by Harrison, Pilcher and Ewing¹⁵ and by Calhoun, Cullen, Clark and Harrison¹⁶. However, there is, as yet, no convincing proof that such chemical changes are

11 Aschoff, L., and Tawara, S. *Die heutige Lehre von den pathologisch-anatomischen Grundlagen der Herzschwache*, Jena, 1906.

12 Christian, H. A. *South M J* **20** 28, 1927.

13 Kutschera-Aichbergen, H. *Wien Arch f inn Med* **18** 209, 1929.

14 Laszlo, D. *Klin Wchnschr* **7** 1411, 1928.

15 Harrison, T. R., Pilcher, C., and Ewing, G. *J Clin Investigation* **8** 325, 1930.

16 Calhoun, J. A., Cullen, G. E., Clark, G., and Harrison, T. R. *J Clin Investigation* **9** 693, 1931.

the sole or even the chief causes of fatigue, although it seems likely that they are in some way related to it

The one outstanding clinical finding in most persons with chronic cardiac disease of various types is enlargement, and similarly the only pathologic changes which are almost invariably present in patients dying of chronic cardiac failure are hypertrophy and dilatation. It is believed that the observations which have been reported in this paper throw some light on the relation of cardiac failure to dilatation and hypertrophy. The studies of Eyster¹⁷ suggest that dilatation, which is the immediate response to increased work (Patterson, Piper and Starling¹⁸), is the cause of hypertrophy, which is generally assumed to be the chronic response to overwork. Some authors hold that hypertrophy in itself constitutes disease. To this point of view we cannot accede, as the evidence for its being a compensatory process seems to us convincing. However, our observations seem to indicate that this compensatory process carries with it a disadvantage, the larger muscle fiber being too thick to admit of the ready diffusion of the necessary oxygen. Fatigue of muscle is generally believed to be due to lack of sufficient oxygen, and the observations which have been reported suggest the conclusion that the increase in fiber thickness is probably an important cause, although by no means the sole cause, of cardiac fatigue.

If this view is correct, it follows that a heart rate much slower than normal would be of great benefit to patients with hypertrophied hearts. This, of course, is merely a hypothesis based on deduction, and its truth or falsity can be demonstrated only by direct evidence. Attempts to secure such evidence are in progress.

SUMMARY

1 A study of ventricular fiber thickness, heart rate and the length of diastole has been made in a number of animals of different species, in normal human subjects of various ages and in human adults with enlarged hearts.

2 In all normal subjects a thick ventricular fiber is associated with a slow heart rate and a thin heart fiber with a fast heart rate.

3 It is believed that the slow heart rate in animals with thick cardiac fibers is advantageous because the recovery period of the heart is prolonged. *i. e.*, it takes oxygen longer to diffuse through a thick fiber than through a thin fiber.

4 Subjects with enlarged hearts have heart rates much faster than would seem to be optimal for such thick fibers.

17 Eyster, J. A. E. *Tr. A. Am. Physicians* **42** 15, 1927.

18 Patterson, S. W., Piper, H., and Starling, E. H. *J. Physiol.* **48** 465, 1914.

5 These observations suggest that "cardiac fatigue" may be due, in part, to a heart rate which is faster than optimal. It is believed that this concept may explain why congestive failure may occur in the absence of any myocardial abnormality other than hypertrophy and dilatation.

6 The data suggest further that if it were possible to reduce the cardiac rate to a level considerably below the normal, "cardiac fatigue" would be much benefited.

SEVERE RENAL INSUFFICIENCY

UNTOWARD EFFECTS OF INTRAVENOUS ADMINISTRATION OF SOLUTION OF SODIUM CHLORIDE ~

E G WAKEFIELD, M D

AND

NORMAN M KEITH, M D

ROCHFSTER, MINN

Two cases are reported herewith of marked renal insufficiency with azotemia and without edema in which the administration intravenously of sodium chloride appeared to produce untoward effects. When the patients came under our observation, it was clearly indicated that if there was anything to be accomplished, it must be done by the intravenous administration of fluids. So far as was known, there were no definite contraindications to administering sodium chloride other than a suspicion that it might do harm. In these cases, the observations were not planned, but they were controlled accurately enough to permit of interpretation.

REPORT OF CASES

CASE 1—A woman, aged 28, a teacher, came to the clinic in September, 1929, complaining of headaches and vomiting. She had enjoyed good health until five months before admission, when she began to have frontal headaches which came on while she was at work. Soon these headaches were accompanied by nausea and later by vomiting. The attacks at first were irregular, and she continued her work until about two and a half months before admission, when the attacks came so frequently that she became incapacitated. She had lost 30 pounds (13.6 Kg) and was very sick.

The patient was pale (hemoglobin, 55 per cent, Dare), weak and low in spirits. There was an odor of urine on the breath. The lungs were clear, the heart was slightly enlarged, and the aortic second sound was definitely accentuated. The systolic blood pressure was 165, and the diastolic, 120 mm of mercury. There was an irregular mass in the region of the right kidney. The reflexes were equal, and there was no edema. The pupils reacted normally. The ocular fundi were pale, the vessels were reduced in caliber, and there was choroiditis in the left eye. Urinalysis showed a trace of albumin and a specific gravity of 1.010.

When the patient was admitted to the hospital, she appeared lethargic, anemic and dehydrated. She weighed 47.2 Kg (chart 1). Renal insufficiency was marked. No phenolsulphonphthalein was excreted in one hour. The blood urea content was 290 mg, and the creatinine, 12 mg for each hundred cubic centimeters, and the effects of vomiting and dehydration were marked. For these reasons the immediate

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* From the Division of Medicine, the Mayo Clinic

* Read before the Central Society for Clinical Research, Chicago, Nov 21, 1930

administration of fluid in large amounts was indicated. Food and fluid taken by mouth were soon vomited. Accordingly, intravenous medication was immediately begun, 1,000 cc of 10 per cent dextrose in 1 per cent sodium chloride solution being given during the first day, and 2,000 cc of 10 per cent dextrose and 1 per cent sodium chloride the second day. In the next five days, from 1 to 2 liters of 10 per cent dextrose was given intravenously daily. The volume of urine gradually increased to 2,400 cc, the patient's weight decreased to 44 Kg, and the blood urea fell to 120 mg. From the eighth to the twelfth day, the fluid administered intravenously contained 1 per cent sodium chloride in addition to 10 per cent dextrose. Twelve days after admission, the patient's weight had increased to 48 Kg, and there was marked clinical improvement. The blood urea was 105 mg for each hundred cubic

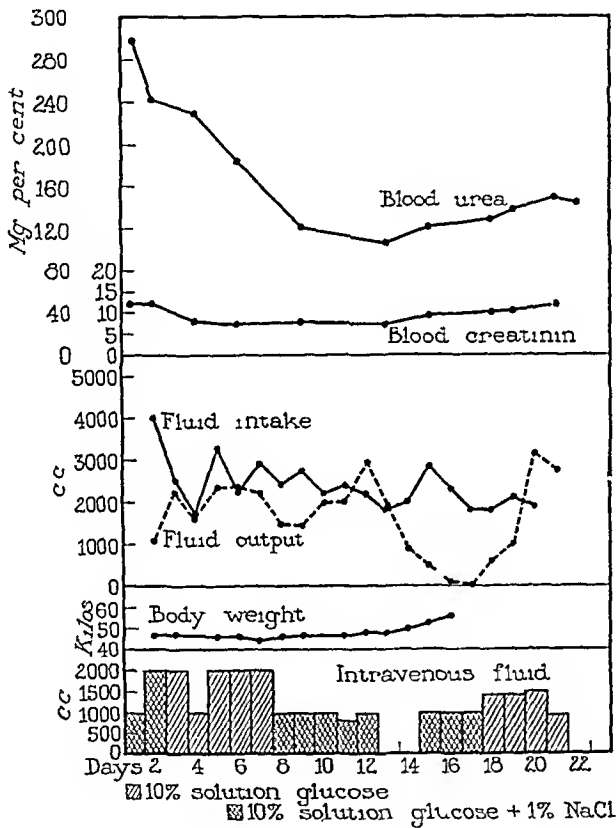


Chart 1—Various effects of the intravenous administration of fluid in case 1

centimeters. For the next two days fluid was not given by vein, and the volume of urine decreased to 900 cc. Intravenous medication was again instituted, and in the following three days the solution contained 10 per cent dextrose and 1 per cent sodium chloride. Oliguria developed and was followed by anuria, lasting for thirty-six hours. The patient's weight had increased to 55 Kg, and edema was noticeable in the face and skin of the lower part of the trunk. The urea and creatinine also increased in the blood. Because of the possibility of the sodium chloride causing the anuria and edema, it was discontinued during the next four days, the intravenous solution containing only 10 per cent dextrose. The excretion of urine was 100 cc during the first day after the appearance of anuria and the total output of fluid was 600 cc, which included 500 cc of vomitus. The volume of urine increased gradually to 2,600 cc on the twentieth day of observation. Even with the restora-

tion of diuresis there was little change in the level of blood urea and of creatinine. During the entire three weeks the patient was in the hospital, urinalysis made as a routine disclosed just a trace of albumin and a specific gravity varying from 1.003 to 1.015, although the daily variation was usually from 1.005 to 1.009. On the twenty-second day of observation, the patient left the hospital. The subsequent course was practically unchanged, for one month, the headache, drowsiness, vomiting and oliguria persisted, then she began to improve slowly. The following April she felt so much better that she considered taking up regular office work. A year after her admission to the clinic, no subjective symptoms were apparent, although her physician was treating her for anemia. Our diagnosis was chronic glomerulonephritis with acute exacerbation and enlargement of the right kidney, the lesion in the latter was not determined.

CASE 2—A man, aged 37, a life insurance agent, had enjoyed good health until the onset of the present illness six weeks before admission to the clinic, on June 13,

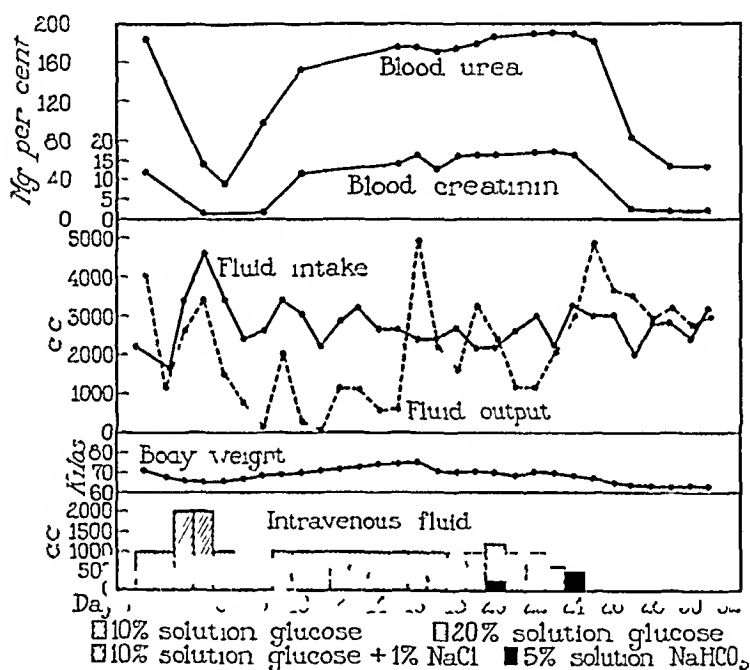


Chart 2—Various effects of the intravenous administration of fluid in case 2

1930. During the first week of May he had some backache and swelling of the right testis. He received four treatments of prostatic massage, which he thought made him feel better. Since January, 1930, he had had nocturia occasionally, which had become worse since the onset of the present illness. During the last two weeks before admission, he had frequency, but no dysuria.

The patient was somewhat anemic (hemoglobin, 50 per cent, Dare), but was well developed and well nourished. The odor of urine on his breath was noted. He did not appear to be critically ill. The tonsils were small, the lungs were clear, the heart was not large, the sounds were regular, and there were no significant murmurs. The systolic blood pressure was 195, and the diastolic, 105, and there was definite peripheral sclerosis. Nothing unusual was found in the genitalia. There was no edema, and the reflexes were normal. The pupils reacted normally. The ocular fundi were essentially normal. Preliminary studies showed that severe renal insufficiency was present, and on June 16 the patient was sent to the hospital for further study.

The striking feature presented by this patient on admission to the hospital was the evidence of serious renal insufficiency with few untoward symptoms. On the second day under observation (chart 2), the blood urea and creatinine were 184 and 124 mg for each hundred cubic centimeters, respectively. Only a trace of phenolsulphonphthalein was excreted in the urine in one hour. Urinalysis showed a specific gravity of 1.011, only a trace of albumin and a few erythrocytes and leukocytes. The patient weighed 71 Kg. Treatment consisted of a diet containing from 1,500 to 2,000 calories, 40 Gm of protein, from 2 to 4 Gm of sodium chloride and from 600 to 2,600 cc of fluid daily. An intravenous injection of from 1,000 to 2,000 cc of a 10 per cent solution of dextrose was given daily. During the first three days, the output of urine was large, in the second period of twenty-four hours amounting to 4,000 cc. On the fourth day, the patient's weight was reduced to 55.7 Kg, and on the fifth day, the content of urea and creatinine in the blood had decreased to 56 and 15 mg for each hundred cubic centimeters, respectively. Intravenous medication was discontinued on the seventh and eighth days. The daily

Studies of the Urine in Case 2

Day of Observation	Specific Gravity	Volume, Cc	Sodium Chloride		Creatinine		Urea Nitrogen		Ammonium Nitrogen		Total Nitrogen	
			Per Cent	Total, Gm	Per Cent	Total, Gm	Per Cent	Total, Gm	Per Cent	Total, Gm	Per Cent	Total, Gm
25	1.013	4,775	0.09	4.29	0.063	2.98	0.21	10.03	0.011	0.53	0.27	12.90
26	1.018	3,650	0.05	1.83	0.105	3.83	0.47	17.15	0.010	0.37	0.56	20.44
27	1.015	3,500	0.04	1.40	0.073	2.56	0.38	13.30	0.026	0.91	0.45	15.75
28	1.012	2,875	0.01	0.29	0.049	1.41	0.31	8.91	0.024	0.69	0.35	10.06
29	1.005	3,050	0.01	0.31	0.040	1.22	0.26	7.93	0.021	0.64	0.30	9.15
30	1.007	2,650	0.01	0.26	0.053	1.41	0.29	7.68	0.020	0.53	0.38	10.07
31	1.008	3,000	0.02	0.60	0.044	1.32	0.31	9.30	0.038	1.14	0.37	11.10
32	1.008	2,250	0.04	0.90	0.062	1.40	0.35	7.87	0.021	0.48	0.41	9.22
33	1.005	3,000	0.02	0.60	0.047	1.41	0.25	7.50	0.013	0.39	0.30	9.00
34	1.006	2,700	0.01	0.27	0.052	1.40	0.27	7.29	0.011	0.30	0.33	8.91
35	1.006	2,700	0.03	0.81	0.052	1.40	0.25	6.75	0.011	0.30	0.33	8.91
36	1.007	3,150	0.04	1.26	0.045	1.40	0.22	6.93	0.007	0.22	0.29	9.13
37	1.007	3,150	0.03	0.93	0.045	1.40	0.21	6.61	0.009	0.28	0.25	7.87

* Albumin was found in the urine only in traces. In all specimens trichloroacetic acid failed to show precipitation. The diet consisted of 40 Gm of protein, 1,500 calories, containing from 2 to 3 Gm of sodium chloride daily.

intake of water by mouth was 2,500 cc, but the volume of urine diminished and the patient's weight increased to 69 Kg. The blood urea rose to 98 mg. Because of recurring renal insufficiency, daily intravenous injections were again instituted, and were continued for the next seven days (the ninth to the fifteenth day). The solution given contained 1 per cent sodium chloride and from 10 to 20 per cent dextrose. The daily volume of urine decreased to 600 cc, and the patient's weight increased to 74.8 Kg. There was no clinical evidence of edema accompanying the retention of water, although there was a marked rise in the blood urea and creatinine to 176 and 164 mg, respectively. The only time vomiting occurred during the patient's illness was on the eleventh and twelfth days, although nausea was occasionally present. In spite of this degree of azotemia, the content of chloride and the carbon dioxide combining power of the plasma were within the normal range. The sodium chloride in the solution given intravenously was suspected of having a harmful effect. On the sixteenth day, the patient was given 1,000 cc of 10 per cent dextrose solution intravenously, and the urinary output amounted to 4,900 cc. The diuresis continued, and the patient's weight fell rapidly to 70 Kg. Contrary to what usually occurs with such marked polyuria, there was no decrease in the azotemia, the blood urea and the creatinine remaining high. These phe-

nomena were similar to those seen on the twentieth and twenty-first days in case 1. There was at this time (twentieth and twenty-third days) a lowering of the alkali reserve of the plasma, the carbon dioxide combining power being 33 and 37 per cent by volume, respectively. Accordingly, on the twentieth and twenty-fourth days, respectively, 200 and 500 cc of 5 per cent sodium bicarbonate solution was administered intravenously. Remarkable diuresis followed the second injection and was accompanied by general clinical improvement, absence of nausea and an increase in the ability to drink water. The weight of the patient steadily decreased, and the content of blood urea and creatinine diminished rapidly. Within a period of six days, the weight had fallen to 63.2 Kg, a loss of 5 Kg, the blood urea from 189 to 54 mg and the creatinine from 16 to 1.9 mg. This marked decrease in the blood urea and creatinine was accompanied by a great increase of these substances in the urine (table).

During the next three weeks, the patient gained in strength steadily. He continued to drink from 2,000 to 3,400 cc of water daily, and the amount of urine varied from 2,300 to 3,900 cc. With these evidences of marked improvement, renal insufficiency was still present, the excretion of phenolsulphonphthalein being 25 per cent in one hour, the blood urea, from 22 to 80 mg, and the creatinine, from 1.9 to 3.6 mg. Because of moderate secondary anemia, a transfusion of 500 cc of blood was given. At the time of dismissal, the patient was feeling well and his weight was 64 Kg, the systolic blood pressure was 155, and the diastolic, 90. He was advised to continue with a diet consisting of 3,000 calories, it included 40 Gm of protein, from 2 to 3 Gm of sodium chloride and from 2,500 to 3,000 cc of water. He was also given ferric citrate for the secondary anemia. A diagnosis of chronic glomerulonephritis with acute exacerbation was made. This patient was seen again in November, 1930. He was doing well and had been at work. The blood urea was 44 mg, and the creatinine was normal.

COMMENT

The two cases presented are of practical significance because they illustrate possible untoward effects from the intravenous administration of too much sodium chloride. Both of these patients had severe renal insufficiency with azotemia and isosthenuria but no edema. The specific gravity of the urine in case 1 ranged frequently around 1.010, and in case 2 around 1.006. Zondek¹ and Volhard² have observed that the concentration of sodium chloride in different samples of isosthenuric urine is inversely proportional to the concentration of nitrogen. This observation has been confirmed by us during one period of observation in case 2 (table). Zondek's and also Volhard's studies were limited to the concentrations of chlorides and nitrogen in the urine without reference to the concentrations of these substances in the blood and possible retention in the body. The oliguria that followed the administration of sodium chloride and the increased diuresis after the administration of

1 Zondek, Hermann. Ueber die Funktion der hamorrhagischen Nierenzündung von Kriegsteilnehmern, *Ztschr f klin Med* **83** 185, 1916.

2 Volhard, Franz. Die doppelseitigen hamatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1918, p 64.

sodium bicarbonate, seen in case 2, indicate the sensitiveness of this patient to different inorganic radicals

Temporary marked renal insufficiency and dehydration may be present in chronic glomerulonephritis. Administration of large amounts of water may have a remarkable beneficial effect. The intravenous injection of fluid may, in certain cases, be imperative, but when the solution contains too much sodium chloride, oliguria and other evidences of increased renal failure may develop. The optimal intravenous solution used by us has been 10 per cent dextrose.

Book Reviews

Die Roentgendiagnostik des Verdauungskanalns einschliesslich der Leber und der Gallenwege By Priv Doz Dr H U Albrecht, Oberarzt an der medizinischen Universitäts-Klinik, Frankfurt, a-M Price, 59 marks Pp 471, with 828 illustrations Leipzig Georg Thieme, 1931

Last year the author published a monograph of seventy-two pages, "Das Ulcus Problem im Lichte moderner Rontgenforschung," which was favorably reviewed in the ARCHIVES (48 169 [July] 1931) The present work enlarges the monograph to include the entire digestive tract The high degree of excellence is retained The illustrations are numerous, well chosen, clear and beautifully reproduced The text is concise and direct, the subject matter seems to be presented by a clinician rather than a roentgenologist The bibliographies are quite complete

The first thirty pages are devoted to the esophagus its anatomy and physiology and the various types of pathologic changes, including foreign bodies, ulcer, diverticulum, varicose veins, benign and malignant strictures, idiopathic dilatation of the esophagus and diaphragmatic herniation Two hundred and fifty pages are employed in a similarly detailed discussion of the stomach and duodenum This section includes the work previously presented in monographic form, and in addition a splendid discussion of gastric syphilis, gastric carcinoma, duodenal diverticula and the stomach on which an operation has been performed The roentgenographic findings in the small bowel and appendix are briefly, but adequately, considered, including Meckel's diverticulum The author thinks that nonvisualization of the appendix is suggestive but not diagnostic, and that much more significance is to be attached to an appendix that is fixed and tender The eighty pages devoted to the colon include a presentation of the anatomy, physiology and pharmacology of the large bowel, as well as a study of its pathology The various methods of examination are described and the results beautifully pictured, the ordinary barium enema, the air inflation method of Fischer, the "Reliefbild" of Knothe and the use of thorium diodysol as attempted by Kalkbrenner The liver is disposed of in a four page discussion of the shadows that are seen on straight films of the abdomen made with and without pneumoperitoneum The latter procedure is described, but is not recommended because the results are dubious and because occasional deaths have been ascribed to it A fifty page consideration of cholecystography concludes the book The author uses both the oral and the intravenous methods of administering tetiothalein sodium (sodium tetraiodophenolphthalein), he attaches little significance to variations in the intensity of the shadow, considers the presence of a shadow prior to the use of tetiothalein sodium as more suggestive of disease than a faint shadow, and lists the following as contraindications to cholecystography cardiac decompensation, severe anemias, cirrhosis of the liver, febrile icterus, exophthalmic goiter, diabetes and chronic nephritis

The work is of the finest quality and is highly recommended

Normale und pathologische Funktionen der Verdauungsorgane im Roentgenbild By Dr Rudolf Becker, Roentgeninstitut des Theresienkrankenhauses, Mannheim, and Dr Albert Oppenheimer, Roentgenabteilung der Med Universitäts-Poliklinik, Frankfurt, a-M Price, 18.75 marks Pp 138, with 255 illustrations Leipzig Georg Thieme, 1931

In this monograph the authors present the results of a detailed study of the motor function of the digestive tract under normal and pathologic conditions The work is unique in that it utilizes the roentgenologic method in an attack on the physiologic problems of gastro-enterology It is instructive, stimulating and well worth reading

The book opens with a brief consideration of the principles of intestinal motility, the types of movement seen and the relationship between motility, tonus and the movement of content. This is followed by a section on the act of swallowing, including its physiologic variations, such as the ability of many people to drink without swallowing. Organic and functional disturbances in the esophagus are adequately considered, cardiospasm and spasm of the esophagus being discussed in well illustrated detail.

The section on the stomach is well done, but it contains little new material. The physiology and pharmacology of the pylorus are discussed, and the conclusion is reached that there are no exact criteria for the diagnosis of pylorospasm as distinguished from simple failure of the pylorus to open.

The two sections devoted to the small intestine and colon are the best in the book. Emptying of the duodenal bulb is ascribed to an active contraction of the bulb running from the tip to the base in a retrograde fashion, the peristalsis being a mirror image of that in the antrum. The action of the ileocecal valve is described in detail, and the motility of the terminal ileum is likened to that of the gastric antrum. Organic lesions of the small bowel are considered, including tuberculosis, adhesions and acute intestinal obstruction. The authors note that in diarrhea the disturbed motility is to be found in the colon, and not in the small bowel, confirming the clinical observations of Strasburger. A careful study has been made of the manner in which barium is carried along through the colon and of the changes observed in diarrhea and in constipation. The normal appendix is said to be visualizable, under proper conditions, in about 90 per cent of cases.

A brief section devoted to the gallbladder presents evidence of active motility of the organ, and describes pathologic conditions in considerable detail.

Clinical Dietetics A Textbook for Physicians, Students and Dietitians

By Harry Gauss, M S, M D, F A C P, Instructor in Medicine, University of Colorado School of Medicine. Assisted by E V Gauss, B A. Price, \$8. Pp 490. St. Louis: C V Mosby Company, 1931.

In his preface, the author states that the book is a presentation in detailed form of lectures on clinical dietetics that he has been delivering for several years. In spite of this, much of the material is given quite briefly. The author demonstrates that he is a student and philosopher, that he has been accustomed to presenting things in a simple form. He has made the subject of dietetics seem relatively easy and interesting. The chapter on diabetes is presented simply and well, but too briefly. The author has striven throughout for simplicity, which often has been accomplished at the expense of the actual facts. The subject matter follows such a definite outline that relatively unimportant things are frequently over-emphasized. Case reports are made to fit into this outline often without adequate justification. This is especially true of the ones used as illustrations of derangements of the digestive secretions. Lists of diets are given generously and constitute the best feature of the book. One general criticism to be made is that too much emphasis is placed on the use of roughage in practically all of the diets.

BACTERIOLOGIC INVESTIGATIONS ON THE BLOOD, SYNOVIAL FLUID AND SUBCUTANEOUS NODULES IN RHEUMATOID (CHRONIC INFECTIOUS) ARTHRITIS

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AND

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The clinical evidence pointing to an infective origin of rheumatoid arthritis has led numerous investigators to seek a bacterial agent to which etiologic significance could be ascribed. A wide variety of such agents has been reported by various workers at various times, but the lack of uniformity in the results obtained has served to confuse rather than to clarify the issue. In recent years the widespread interest in rheumatoid arthritis and the recognition of the social and economic importance of this disease have stimulated renewed activity in the search for the etiologic agent.

HISTORICAL

Bacteriologic studies on the blood and tissues in rheumatoid arthritis are so numerous that a complete review of the results obtained is not within the scope of this report. Moreover, a critical review of the literature is difficult, for numerous investigators have presented the results obtained without reference to the technic employed, the kind of cases investigated or the methods adopted for the identification of the organisms found. Extensive reviews¹ of the literature have recently appeared from which the résumé presented in table 1 has been abstracted. The

* Submitted for publication, May 25, 1931.

[†] From the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Arthritis Clinic of the Presbyterian Hospital (the Arthritis Clinic of the Presbyterian Hospital is supported by the Faulkner Memorial Fund).

[‡] The Arthritis Clinic of the Presbyterian Hospital has adopted the classification and nomenclature for rheumatic diseases provisionally recommended by the British Ministry of Health and the International League for the Control of Rheumatism. In this classification the term "rheumatoid arthritis" is used to designate that form of chronic multiple arthritis more commonly called "chronic infectious" or "atrophic" in America.

¹ Pathogenic Streptococci, Ann Pickett-Thomson Research Lab pt 2, 4 253 (April) 1929. Jordan, E P. Microbic Etiology of Rheumatic Fever and Arthritis, Arch Path 10 79 (July) 1930.

TABLE 1—*Results of Bacteriologic Study Recorded in the Literature*

Author	Year	Tissue Cultured	Number Cases	Results
Schuller	1892 1906	Synovial fluid and joint tissues	230	Gram positive diplobacillus in 150 cases
Bannatyne, Wohlman and Blavall	1896	Synovial fluid	18	Gram negative diplobacillus (by smear) in all instances
Crawford and Mallin	1903	Synovial fluid	48	Majority sterile few positive cultures considered accidental contamination
McCrae	1904	Synovial fluid	110	Negative
Davis	1912	1 Blood and synovial fluid 2 Tonsillar crypts	14 42	Negative Streptococcus hemolyticus 28
Rosenow	1914	Regional lymph glands	54	Streptococcus viridans 32 Bacillus welchii 14 Staphylococcus 5 Diphtheroid bacillus 5 Bacillus mucosus 3 Micrococcus catarrhalis 1 Gonococcus 1 Sterile 7
Rowlands	1914 1915	Blood and synovial fluid	40	Negative
Moon and Edwards	1917	Blood and synovial fluid	83	Nonhemolytic streptococcus 18 (other organisms occasionally found)
Richards	1920	1 Blood 2 Synovial fluid	104 54	Streptococcus viridans 14 Streptococcus viridans 4
Munro	1922	Synovial fluid	50	Gram positive coccus (with little hemolysis and little decoloration) 4
Billings, Coleman and Hubbs	1926	Joint tissue	14	Streptococcus viridans or nonhemolytic 5 Streptococcus hemolyticus 1 Mixed 1
Hadjopoulos and Burbank	1927	Blood	145	Streptococcus hemolyticus 9 Streptococcus viridans 6 Diphtheroid bacillus 8 Staphylococcus aureus 5
Suranyi and Forro	1928	Blood	25	Streptococcus viridans 19
Forkner, Shands and Posten	1928	1 Synovial fluid 2 Regional lymph glands	63 21	Streptococcus viridans 11 Gonococcus 2 Staphylococcus aureus 1 Streptococcus viridans 9 Gonococcus 1
Posten	1929	Regional lymph glands	120	Streptococcus viridans 67 Streptococcus nonhemolyticus 2 Staphylococcus aureus 2 Gonococcus 1
Cecil, Nicholls and Stainsby	1929	Blood	78	Streptococci, (83%, "attenuated hemolytic") 48
Margolis and Dorsey	1930	Blood	89	169 blood cultures (1) 68 following technic of Cecil, Nicholls and Stainsby Streptococcus viridans 3 Diphtheroid bacillus 2 (2) 74 following authors' own technic Streptococcus viridans 4
Nye and Waxelbaum	1930	1 Blood 2 Synovial fluid and lymph glands	21 5	Negative Inconsistent

results reported by Margolis and Dorsey² and by Nye and Waxelbaum³ are included in the summary

From table 1 it is apparent that there is no unanimity of opinion as to the specific etiology of rheumatoid arthritis. Three alternative explanations may be offered to account for the wide variety of findings recorded

² Margolis, H. M., and Dorsey, A. H. E. Bacteriology of Blood in Chronic Infectious Arthritis, *J. Infect. Dis.* **46**: 442 (June) 1930

³ Nye, R. N., and Waxelbaum, R. A. *J. Exper. Med.* **52**: 885, 1930

1 Rheumatoid arthritis may not be the result of infection by one particular bacterial agent but rather by a multiplicity of such agents

2 The bacteria recovered may or may not be of etiologic significance, and, in either case, may represent only casual invasion of the blood stream and joint tissues from a distant focus

3 The organisms recovered may not actually be present in the body fluids, but may be the result of contamination due to imperfect technic

The remarkable results recently reported by Cecil, Nicholls and Stainsby⁴ on the bacteriology of the blood and joints in rheumatoid arthritis are of particular interest. These authors, by the use of a special technic, claimed to have demonstrated the presence of streptococci in the blood stream in 61.5 per cent of a series of 78 patients examined. They reported that 83.3 per cent of the strains recovered are culturally and biologically identical and appear to be "attenuated hemolytic streptococci." They also reported that a streptococcus culturally and biologically identical with the strain isolated from the blood can sometimes be cultivated from one of the affected joints of the same patient.

Because of the unusual nature of this report and the importance of such an observation in the study of rheumatoid arthritis the present investigation was undertaken. A preliminary report of the results of this investigation has recently been presented.⁵

During this study all possible assistance was extended to us by Drs. Cecil, Nicholls and Stainsby. They permitted us to study the technic as carried out at Bellevue Hospital, and the early portion of the work was done in their laboratory. Broth was supplied by Dr. Nicholls for a portion of this investigation.

METHODS

The greatest care was exercised to follow the technic described by Cecil, Nicholls and Stainsby. This technic, as described in their original article,⁴ is as follows:

The technic employed for blood cultures was an adaptation of that recommended by Clawson in his blood culture studies of rheumatic fever.

Twenty cubic centimeters of blood was taken aseptically from the arm with a Luer syringe, placed in two sterile culture tubes and allowed to clot. Each tube was treated separately in the following way:

The tube was centrifugated, and all the serum drawn off with a sterile pipet. The clot was then broken up in the original culture tube with a sterile glass tube, $\frac{1}{4}$ inch (6.35 mm) in diameter. The fragments of clot were drawn up in the same glass tube, and transferred to a 3 ounce bottle containing 50 cc. of beef heart infusion broth with a p_H of 7.6 (0.5 per cent sodium chloride, 1 per cent peptone).

4 Cecil, R. L., Nicholls, E. E., and Stainsby, W. J. Bacteriology of Blood and Joints in Chronic Infectious Arthritis, *Arch. Int. Med.* **43**: 571 (May) 1929.

5 Dawson, M. H., Olmstead, M., and Boots, R. H. *Proc. Soc. Exper. Biol. & Med.* **28**: 419, 1931.

The bottle was then put in the incubator at 37 C and left there unopened for five days

At the end of this time, a tube containing 8 cc of a 15 per cent beef heart infusion agar was placed in the water bath and heated until the agar was completely melted. The tube was then partially cooled and 0.5 cc of whole rabbit blood added to it. Finally, the tube was seeded with 0.1 cc of broth from the original blood culture, and the contents poured into a petri dish. The culture was allowed to incubate for from twenty-four to forty-eight hours. Similar pour-plate cultures were made every three to five days thereafter until the original blood culture had been in incubation for thirty days. If, at the end of this time, the subcultures were still sterile, the sediment in the original blood culture bottle was drawn out with a sterile glass tube and centrifugated. After centrifugation, part of the sediment was examined by means of stained smears, while the remainder was cultured, part of it in fresh blood broth and part of it on blood agar plates. If these final cultures from the sediment showed no growth, the blood culture was considered sterile.

All of these cultures and transfers were made under a hood, in order to eliminate contaminations as far as possible. All contaminated cultures were discarded.

When colonies appeared on the plates, they were transferred into blood broth and identified by the usual bacteriologic methods.

Examination of this technic shows that the average number of manipulations involved in the procedure was as follows:

Taking of blood	1
Separation of clot	1
Centrifugation	1
Pipetting off serum	1
Breaking up clot and transferring to flask	1
Opening of flasks to obtain samples for plates	6
Centrifugation of sediment	1
Pipetting off supernatant fluid from sediment	1
Streaking plate from sediment	1
Making smear from sediment	1
Adding blood broth to sediment	1
Subculturing sediment cultures	2
	—
Total number of manipulations	18

The second sample of blood was, as a rule, subjected to a smaller number of manipulations inasmuch as plates were not poured from it until cultures of the first sample either showed growth or remained sterile for the full period of thirty days. The average number of manipulations to which the second specimen was subjected was approximately 14.

These 14 to 18 manipulations, extending over a period of six weeks, constituted the average number to which all cultures were subjected. It is therefore not surprising that a considerable number of contaminations were encountered in the course of this study. The occurrence of all bacterial growth, including even the most obvious contamination, is recorded in the work herewith presented.

THE PRESENT STUDY

In the present investigation blood cultures were done only according to the technic described by Cecil, Nicholls and Stansby. The relatively large amount of blood required and the intricacies of the procedure precluded a more extensive investigation by other cultural methods with other nutrient mediums. It is therefore emphasized that the conclusions drawn from this investigation apply only to the narrow range of cultural methods employed.

The type of patient selected presented a characteristic clinical syndrome with chronic polyarthritis, frequently accompanied by swelling and deformity of the joints affected. The great majority of cases chosen for study were in the active stage of the disease. Cases of osteoarthritis (hypertrophic, degenerative) were not included in the investigation. The study extended over a period of twelve months from March, 1929, to March, 1930. The possible effect of seasonal variations was therefore eliminated.

In the course of the investigation 105 separate blood cultures were done on 80 patients. In the majority of instances the specimens of blood obtained at each venipuncture were divided into two portions, so that in all 204 samples of blood were cultured. In 18 selected patients cultures were made on two occasions, in 3 on three occasions and in 1 on six occasions.

Control Material—In order that correct conclusions might be drawn from the occurrence of bacterial growth in the blood cultures of arthritic patients, 31 samples of blood were obtained from 16 normal persons and subjected to similar methods of culture. By way of further interest, 16 tubes of sterile autoclaved agar were subjected to the same manipulations and cultured by the same technic as that described by Cecil, Nicholls and Stansby.

The results of these investigations are presented in the following tables.

TABLE 2—Summary of Blood Cultures on Patients with Rheumatoid Arthritis

Number of blood cultures	105
Number of samples of blood	204
Number of patients	80
Of the 204 samples of blood	146 (72%) remained sterile, 58 (28%) yielded growth
Organisms recovered	
Gram positive bacillus (coarse)	21
Diphtheroid bacillus	13
Staphylococcus	17
Streptococcus viridans	2
Streptococcus anhemolyticus	1
Gram positive coccus (exact nature undetermined)	2
Mold	2
	<hr/> 58

In addition, colonies of bacteria occasionally appeared in the pour-plates, but their presence in the flask was not established. These colonies

were composed of a wide variety of organisms comparable to those recovered from the flasks. A few colonies of *Streptococcus viridans* and *Streptococcus anhemolyticus* appeared on three occasions.

Each specimen, on the average, was subjected to 15 manipulations, or 3,075 manipulations for the entire series.

Colonies of a variety of bacteria also occasionally appeared in the pour-plates, but their presence in the flask was not established.

Each sample, on the average, was subjected to 15 manipulations, or a total of 465 manipulations for the entire series.

In addition, one pour-plate showed 10 colonies of *Streptococcus viridans*, but subsequent platings from the same flask remained sterile.

Each specimen, on the average, was subjected to 18 manipulations or a total of 228 manipulations for the entire series.

TABLE 3—*Summary of Blood Cultures on Control Subjects*

Number of blood cultures	16
Number of samples of blood	31
Number of subjects	15
Of the 31 samples of blood 27 (87%) remained sterile, 4 (13%) yielded growth	
Organisms recovered	
Gram positive bacillus (coarse)	1
Diphtheroid bacillus	1
Staphylococcus	1
Mold	1
	<hr/> 4

TABLE 4—*Summary of Cultures of Samples of Sterile Agar Subjected to Similar Manipulations*

Number of samples of sterile agar	16
Of the 16 samples 12 (75%) remained sterile, 4 (25%) yielded growth	
Organisms recovered	
Diphtheroid bacillus	2
<i>Streptococcus viridans</i>	1
Gram positive coccus (coarse, air?)	1
	<hr/> 4

The results of (1) blood cultures on patients suffering from rheumatoid arthritis, (2) blood cultures on normal persons and (3) cultures of specimens of sterile agar subjected to similar manipulations, according to the technic of Cecil, Nicholls and Stainsby, have led to the following conclusions:

1 In spite of the greatest care to perform all manipulations under sterile precautions, the technic, in our experience, was so involved as to call into serious question the significance of all bacterial growth encountered.

2 Blood cultures on patients suffering from rheumatoid arthritis failed to yield results that could be considered of etiologic significance.

3 No essential difference was found in the bacteria encountered in the three groups of material cultured.

4 The appearance of typical *Streptococcus viridans* on two occasions during the culture of specimens of sterile agar, subjected to similar manipulations, was felt to be of significance

JOINT CULTURES

While the scope of the present investigation was primarily confined to the study of blood cultures, the bacteriology of the synovial fluid of a number of patients suffering from rheumatoid arthritis was also investigated. In the majority of cases the synovial fluid was withdrawn from the knee joint, but occasionally a small amount was obtained by aspiration of the wrist joint, the ankle joint and the proximal interphalangeal joints of the fingers.

The synovial fluid was withdrawn under sterile precautions and cultured in a variety of mediums which included the following: blood broth, hormone broth, meat broth, dextrose ascitic broth, and dextrose ascitic agar shakes. The meat broth was heated in a water bath at 100 C for twenty minutes and allowed to cool to body temperature before being inoculated. The cultures in the dextrose ascitic agar shakes were carried out under petrolatum seal. In some cases the amount of fluid available was insufficient for culture in all the mediums mentioned. In other cases, when more material was available, all the nutrient mediums named were employed and varying amounts of synovial fluid were cultured in the same medium. All the cultures were kept in the incubator at 37 C for at least thirty days and carefully examined for the presence of bacterial growth at four or five day intervals during that time. This procedure greatly added to the number of manipulations and naturally increased the probability of contamination. In all, 23 samples of joint fluid, obtained from 19 patients, were examined by this technic, with the following results: gram-positive bacilli (coarse), 3; diphtheroid bacilli, 3; and staphylococci, 1.

Because of the variety and nature of the organisms encountered and because of the possibility of contamination in cultures subjected to repeated manipulations over such a prolonged period, it was felt that no etiologic significance could be attached to the results obtained.

CULTURES ON SUBCUTANEOUS NODULES

It has been pointed out in previous communications⁶ that subcutaneous nodules are of not infrequent occurrence in patients suffering from rheumatoid arthritis. Such nodules were observed in 43 patients who presented themselves for treatment at the Arthritis Clinic of the

6 Dawson, M. H., Sia, R. H. P., and Boots, R. H. *J. Lab. & Clin. Med.* **15** 1065, 1930. Dawson, M. H., and Boots, R. H. *Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis*, *J. A. M. A.* **95** 1844 (Dec 20) 1930.

Presbyterian Hospital during the past eighteen months. Sections were obtained on 16 of these nodules and the material was subjected to careful pathologic investigation. All the material examined showed a uniform and highly characteristic histologic structure.⁷ For these reasons particular attention was directed toward the bacteriologic study of the subcutaneous lesions of this disease.

Sixteen nodules, obtained from 11 patients, were cultured in a variety of mediums which included the following: blood broth, meat broth and dextrose ascitic agar. Whenever sufficient material was available, cultures were carried out anaerobically as well as aerobically. All cultures were kept in the incubator at 37 C. for at least thirty days and carefully examined every few days for the occurrence of bacterial growth. The results of these cultures were as follows: diphtheroid bacilli, 3, and staphylococci, 2.

Sections of the subcutaneous nodules were stained by Gram's method and carefully examined for the presence of bacteria. In no case was it possible to demonstrate the occurrence of micro-organisms in the characteristic subcutaneous lesions of this disease.

For the same reasons as those enumerated in the case of the joint cultures, it was felt that no etiologic significance, other than that of a negative character, could be attached to the results obtained.

SUMMARY

1 One hundred and five blood cultures, the majority in duplicate, were carried out on 80 patients suffering from rheumatoid arthritis according to the technic of Cecil, Nicholls and Stainsby. As control material, 31 samples of blood from normal persons and 16 samples of sterile autoclaved agar were subjected to similar manipulations.

2 The blood cultures on patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

3 No significant difference was observed in the bacteria encountered in the blood cultures of patients and those observed during the culture of the control material under similar conditions.

4 *Streptococcus viridans* was occasionally encountered during the culture of the control material as well as during the culture of specimens of the patients' blood.

5 Aerobic and anaerobic cultures of 23 specimens of synovial fluid obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

6 Aerobic and anaerobic cultures of 12 subcutaneous nodules obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

⁷ Dawson, M. H., and Pappenheimer, A. M. *Scient. Proc., Am. Soc. Path. & Bact.*, April, 1930.

BASAL METABOLISM

I THE ERROR OF BASAL METABOLISM DETERMINATION AND THE NORMAL RANGE OF BASAL METABOLISM^{*}

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The error of basal metabolism determination is of interest clinically chiefly as it affects the usefulness of basal metabolism determination as a diagnostic procedure. It may then be expedient to begin a study of this error with a consideration of the "normal range of basal metabolic rates," and to pass from this to a discussion of the error of determination and its implications.

For a proper evaluation of the "normal range of basal metabolic rates" it is necessary to know two things. The first is a measure of the central tendency of the metabolism of normal persons. This will be referred to in this paper as the "zero point." The second is a measure of the spread of the basal metabolism of normal persons about this "zero point"—a measure of the dispersion of the distribution. These factors will be discussed separately.

THE ZERO POINT

Every metabolism standard has a zero point. The most obvious solution of the quest for the zero point is to accept the zero point of the standard used as the true zero point. But when one realizes that the zero point of two different standards for adults may differ by as much as 9 per cent,¹ it becomes apparent that this cannot be generally satisfactory. The situation with regard to children's standards is considerably worse.

There are differences in the level of metabolism of groups of normal subjects reported by various investigators not explainable by chance but reflecting either real differences in the populations studied or differences in technic such as would result in finding rates consistently higher in one laboratory than in another. A discussion of which of these two explanations is the more likely is outside the scope of this article. *The point of importance is that such differences do exist, and that they preclude the use of the zero point of a particular standard as a true zero point of a particular population and laboratory without experimental verification.*

Submitted for publication, May 18, 1931

This study was carried out under the auspices of the Social Science Research Committee of the University of Chicago

1 Difference in the zero points of the Krogh and the Mayo standards for men

Using a portable Benedict apparatus modified by the Sanborn motor blower, I found the zero point (defined as the mean rate) of a group of thirty-four apparently normal male university freshmen to be —5 per cent, according to the Aub-DuBois standard. With the same type of apparatus, members of the staff of the metabolism laboratory of the University of Chicago Clinics, under the direction of Miss Majorie Smith, made determinations of basal metabolism of 1,126 men and 2,994 women, between January, 1929, and September, 1930,² the distributions found are shown diagrammatically in charts 1 and 2. It will be noted that the peak of each distribution is within the normal range, and that each distribution is skewed to the right (in the direction of high rates). This is to be expected, as at least in this locality "hyperthyroidism" is far more common than hypothyroidism. It is

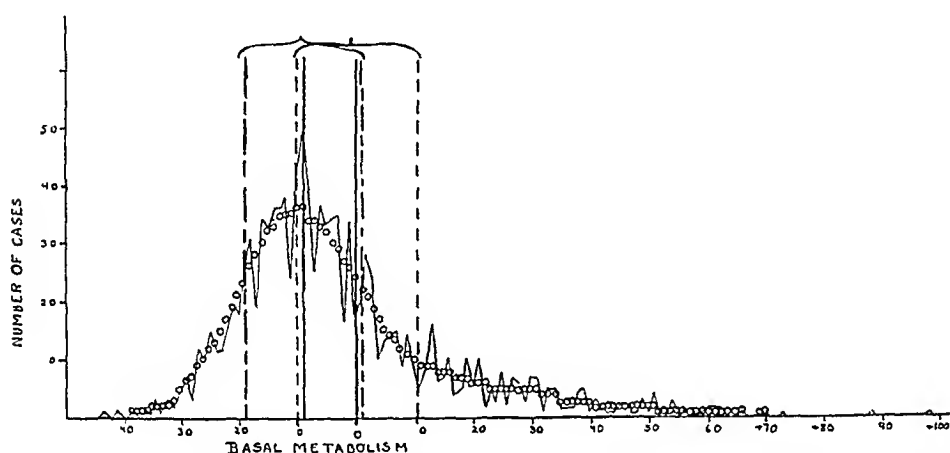


Chart 1—Distribution of basal metabolism of 1,126 men. These determinations were made in the University of Chicago Clinics.

reasonable to suppose that in that section of the distribution which is within the normal range, there is a preponderance of normal persons, i. e., of those normal with regard to metabolism. If there is such a preponderance of persons with normal metabolism, the greatest number should fall at the zero point. It will be noted that in the case of both men and women the peak of the original curve and the peak of the smoothed curve for women falls at —9 per cent. The smoothed curve for men is equally high at —9 per cent and —10 per cent. The difference between —5 per cent and —9 per cent is in part accounted for by the fact that in my data on normal persons, successive determinations on a given day were averaged, while in the data of the clinic the lower reading was selected. This accounts for a discrepancy of from 2 to 2.5 per cent. The remainder is within easy chance.

² The Department of Medicine, University of Chicago Clinics, permitted me to use this material.

deviation, in view of my short series. If the value of the clinic is accepted and successive determinations are averaged, the zero point for this particular locality and technic is -7 per cent. If the lower reading is selected, the zero point is -9 per cent. The importance of the location of the zero point may be realized better if one considers that the conventional 21 per cent range being used as the "normal range" about the zero point, the "normal range" in the data of the clinics may be defined as from -19 per cent to $+1$ per cent instead of from -10 per cent to $+10$ per cent. This would result in a shift of 38 per cent of the women and 37 per cent of the men one way or another across the "limit of the normal range." Incidentally, as a result of such a change, 57 per cent of the women would fall within the normal range in place of 49 per cent and the percentage of men with "normal" rates

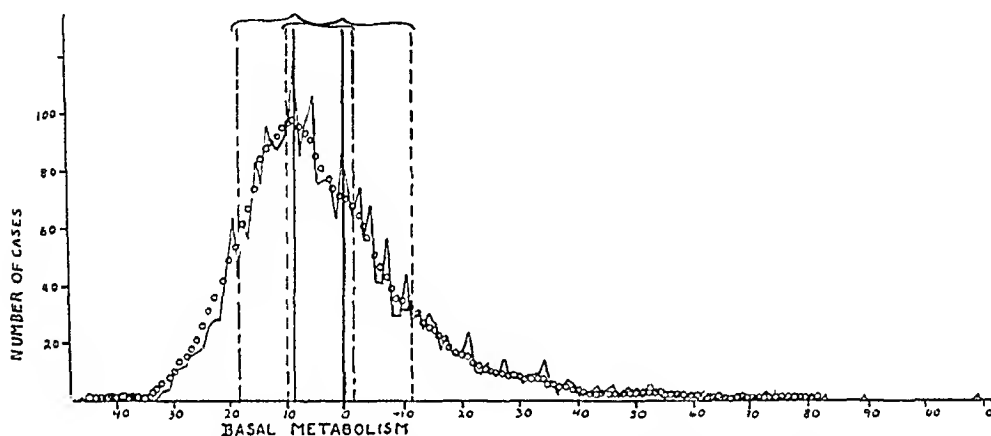


Chart 2—Distribution of the determinations of basal metabolism of 2,994 women. A portable Benedict apparatus modified by the Sanborn motor blower was used.

would be increased from 45 per cent to 57 per cent. The limits -10 per cent, $+10$ per cent, -19 per cent and $+1$ per cent are indicated on figure 1 and 2.

It may be well here to emphasize that it is highly desirable that each laboratory should individually determine its zero point by the standard it uses. Such a determination should be based on not less than twenty-five normal persons. The determination of the modal point of the distribution of basal rates on a large series of unselected patients may be regarded as a substitute method more open to criticism.

THE NORMAL DISPERSION

It is in a consideration of the "normal dispersion" that the question of random errors of technic must enter. Constant errors will have been taken care of by an adjustment of the zero point. If it were possible to achieve an ideal state, the "normal dispersion" would be reduced

to zero, and the metabolism determinations of all normal persons would fall at the zero point. Under such circumstances, a deviation of 1 per cent from the zero point might be branded as pathologic. This would imply a perfect technic of measurement of gaseous exchange, a perfect "basal state" in every normal person, a perfect normal standard and a perfect application of this standard to each individual. By perfect standard, I mean a standard that would predict exactly the metabolism of any normal individual under the foregoing circumstances. Such a standard lies beyond hope of even ultimate achievement. Experience indicates that under the most favorable conditions one must expect a certain normal dispersion—a dispersion of the metabolism of normal persons, which will certainly remain with the best standard that can ever be devised and the best technic one may ever hope to introduce. Let me here introduce the concept of a true normal dispersion—the dispersion that would remain among "normal" persons if there were a perfect technic, the best possible standard and a constant basal state. Such a true normal dispersion would be less than the normal dispersion that one experimentally observes. The latter is greater because in it one adds the effects of imperfect technic, imperfect standard, imperfect application of the standard (errors in measurement of height and weight) and the fact that a constant "basal condition" is not achieved. These factors all widen the experimental normal dispersion and thereby blunt the technic as a clinical instrument. I proceed, therefore, to a consideration of their influence on the experimental normal dispersion and of how they may be kept at a minimum. I shall choose the standard deviation (σ) as the measure of dispersion.

Then $\sigma_n' = f(\sigma_n, \sigma_t, \sigma_s, \sigma_m, \sigma_b)$, in which σ_n' represents the standard deviation of the experimental normal dispersion, σ_n represents the standard deviation of the true normal dispersion as here defined, σ_t represents the standard error of the technic of measurement of gaseous exchange (or of direct calorimetry), σ_s represents the standard error of the relative prediction value of the standard, σ_m represents the standard error of the application of the standard, and σ_b , the coefficient of variation in the metabolism of normal persons under the condition of basal metabolism determination.

I have indicated that the sharpening of the diagnostic instrument depends on reducing the experimental normal dispersion until it approaches as closely as possible the true normal dispersion. This depends on reducing to as low a level as possible the various errors appearing in the latter part of the expression. I shall consider these separately.

The errors of technic have been the subject of many articles. There is widely a proper respect for them, and effort is directed, with varying

degrees of intensity and success, to their elimination. The importance of this effort is self-evident.

The errors of the standards have been neglected to a greater extent. Table 1, which is condensed from a previous article,³ contains a tabulation of the coefficient of variation of the error of relative prediction of the basal metabolism of normal persons by the Aub-DuBois standard, the Harris-Benedict standard and the Dreyer standard based on observed weight. It should be noted that these are the errors of relative prediction and not of absolute prediction, each deviation is measured, not from the zero point of the standard, but from the zero point of the group of normal values experimentally determined by this standard. It should further be noted that what actually enters into the determination of normal dispersion is not the coefficient of variability of $\frac{\text{observed calories}}{\text{predicted calories}}$, but the coefficient of variability of $\frac{\text{predicted calories}}{\text{observed calories}}$. The two values may be expected to be practically identical, however, and for the purposes of this comparison this difference is ignored. It will be noted that the Harris-Benedict standard and the Dreyer standard are rather better than the DuBois standard in their accuracy in relative prediction. The weighted mean of the coefficients of variation of the Aub-DuBois standard is 7.505, while the value for the Harris-Benedict standard is 6.605 and that for the Dreyer standard, 6.805. This is a significant improvement.

In the material surveyed by me, the standard of Harris and Benedict, the Dreyer standard based on observed weight and the Boothby and Sandiford standards appear the best by empirical test. The Harris-Benedict standard has the advantage of widely established usage in this country and on the continent of Europe. It necessitates the use of another standard for children. The Dreyer standard and the Boothby-Sandiford standard are applicable to children as young as 5 years of age. The Dreyer standard has an established usage particularly in England. If one uses the tables of Stoner,⁴ it is the easiest standard of all to apply.

There is a further procedure by which it is possible to reduce the part played by the error of standard. This consists in the calculation of all borderline or doubtful rates by two or three standards, as this will frequently make a difference of several per cent in the basal rate, even after allowance is made for the differences in the level of the standards. In carrying out this procedure, due allowance should be made for the difference in the level of the standard. Such allowance is conveniently made by the use of tables that I have published.

3 Jenkins, R. L. Basal Metabolism Standards, *J. Nutrition* **4**: 305, 1931.

4 Stoner, W. H. Notes on Basal Metabolism, V and VI. Tables of Values of Dreyer's Formulas, *Boston M. & S. J.* **189**: 239, 1923, **191**: 1026, 1924.

The error in the application of the standard should be slight, if ordinary care is used. It is not difficult to determine height and weight with a satisfactory degree of accuracy. However, the use of the Dreyer standards based on calculated weight increase these errors materially, as Miss Boyd⁵ has pointed out.

The error introduced by the actual variation in the metabolism of a given normal person may be considerable. Wishart⁶ found it to be usually in the neighborhood of 5 per cent (coefficient of variation = 5). In my experience with university freshmen, and in the extensive experi-

TABLE 1—Probability of Deviation of Normal Persons

Deviation From Zero Point, per Cent	Probability
5	1 chance in 4
10	1 chance in 13
15	1 chance in 63
17	1 chance in 132
20	1 chance in 455

TABLE 2—Prediction Accuracy of Various Standards on Adults

Investigator	Number of Subjects	Sex	Coefficient of Variation*		
			Aub Dubois Standard	Harris Benedict Standard	Dreyer Standard (Observed Weight)
Harris and Benedict	134	M	8.59	6.10	6.53
Harris and Benedict	102	F	7.82	7.85	7.68
Boothby and Sandiford	41	M	6.19	5.95	5.96
Boothby and Sandiford	61	F	5.59	5.85	6.17
Earle	87†	M	7.13	6.59	6.85
Hobson	46	M		7.19	6.10
Author	34	M	8.27	7.04	7.11
Mean (excluding Hobson)			7.265	6.503	6.725
Mean (excluding Hobson) weighted for number of cases			7.505	6.605	6.805

* Coefficient of variation of $\frac{\text{predicted calories}}{\text{observed calories}}$
† These subjects were Chinese

ence of Dr Kunde of this university with dogs, there is considerable difference between persons in the extent to which their metabolism tends to vary. This source of error is reduced to a minimum by observing carefully the standard procedures for inducing a basal condition and by making repeated tests in doubtful cases, training the subjects to relax.

Any definition of "normal range of basal metabolism" is necessarily arbitrary. There is, of course, a gradual diminution in the likelihood

5 Boyd, Edith. The Experimental Error Inherent in Measuring the Growing Human Body, *Am J Phys Anthropol* **13** 389, 1929.
6 Wishart, George. The Variability of Basal Metabolism, *Quart J Med* **20** 193, 1927.

that a given person's metabolism is normal, as our measurement shows it to deviate from the zero point. If 7 is accepted as a typical coefficient of variation of the basal metabolic rates of normal persons tested with careful technic, the probability is that a normal person will deviate any given distance in a given direction from the mean, as tabulated in table 1. It is obvious that a normal range of 10 per cent is dangerously small, as two normal persons in thirteen may be expected to fall outside the normal range, one at either end.

Of course, the same series of normal persons used to determine the "zero point" in any given laboratory may also be used to determine the normal dispersion for that laboratory by a calculation of the coefficient of variation. Chance factors in the selection of "normals" will enter into the coefficient of variation unless a fair series is used.

SUMMARY AND CONCLUSIONS

- 1 Every laboratory should determine the "zero point" of its own normal population and its own technic on the standard it uses. This may be carried out by determinations on a minimum of twenty-five normal persons or by taking the modal point of a very large series of unselected cases.

- 2 The experimental normal range is a function of the true normal range and the errors of measurement. With good technic, it is possible to reduce the normal range to a minimum and so sharpen basal metabolism determination as a diagnostic instrument.

- 3 The use of the Harris-Benedict standard or the Dreyer standard based on observed weight reduces the normal range as compared with the Aub-DuBois standard.

- 4 The error introduced by the standard may be further reduced by comparing two or three standards in all doubtful cases.

- 5 A delimitation of the normal range to 21 per cent is probably overly low, even with a good technic. This might be supplemented by regarding all cases deviating from 10 to 17 per cent from the zero point as "doubtful."

BASAL METABOLISM

II THE BASAL PULSE COMPLEX *

R L JENKINS, M D

CHICAGO

The importance of the elevation of pulse rate and pulse pressure in the diagnosis of disturbances of the thyroid has long been recognized. Despite the importance of these symptoms and the fact that they are easily available to quantitative treatment, their clinical use is largely by rule of thumb. Since their value is so generally recognized by rule of thumb methods, it seems not unreasonable to suppose that it might be considerably increased by the application of more precise methods of study and use.

In 1924, Read published a formula for the prediction of basal metabolism from basal pulse rate and basal pulse pressure¹. The formula is $0.75 (\text{pulse rate} + 0.74 \text{ pulse pressure}) - 72 = \text{basal rate}$. Read stated that by this formula it was possible to predict the basal metabolic rate within 10 per cent in a little more than half of the cases.

Hunt compared basal rate and Read's formula in 54 cases. Four basal determinations were rejected as unreliable. Of the remaining 50 cases, in 27 (54 per cent) the basal rate and the value from Read's formula agreed within 10 per cent. Hunt is quoted by Langmead² as drawing the following conclusions:

1 Read's formula will very seldom give appreciably too high an estimate of the basal metabolic rate, but often gives slightly lower figures.

2 A very marked discrepancy suggests an error in technique.

3 The basal metabolic rate in very bad cases is probably fairly considerably higher than Read's formula suggests.

4 Iodine treatment appears to improve the circulatory system as shown by Read's formula more definitely and more permanently than it improves the basal metabolic rate, which does not appear to be reduced for long by the comparatively small doses given (up to 20 minims of Lugol's solution daily). With this exception Read's formula has shown improvement in treatment exactly parallel with that shown by the basal metabolic rate.

Submitted for publication, May 18, 1931

* This study was carried out under the auspices of the Social Science Research Committee of the University of Chicago.

1 Read, J. Marion. Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in Basal Metabolic Rate, *Arch Int Med* **34** 553 (Oct) 1924.

2 Langmead, F. S. The Etiology, Prognosis and Treatment of Graves' Disease, *Brit M J* **1** 715, 1929.

5 Read's formula should be applied under basal conditions but does not seem to vary so much as the basal metabolic rate from food or other external factors. In some cases it is quite impossible to gauge this latter accurately. Within limits it would seem that the figure obtained by this formula is an accurate guide to progress, and differs widely from the basal metabolic rate figure only in the severest cases. It has a particular field of usefulness when for some reason estimation of the basal metabolic rate is not practicable.

In view of the fact that it is a quite widespread practice to take the pulse under basal conditions at the time the basal metabolism is determined, and that it is very simple to add a determination of blood pressure, it seems strange that this formula has not come into rather general use in connection with the actual determination of basal metabolism. Its value by such an arrangement would not lie in predicting the basal rate, since this can be experimentally measured with considerably more accuracy, but rather in affording a "pulse complex" figure which would be directly comparable with the basal rate and afford a confirmatory diagnostic measure.

SOURCE OF MATERIAL

The material used for this study consists of 4,120 routine basal metabolism determinations. These determinations comprise all of the determinations made on subjects 16 or more years of age in the metabolism laboratory of the University of Chicago Clinics from January, 1929, to September, 1930. All determinations were made by or under the direction of Miss Marjorie Smith who was in charge of the laboratory. This material has been used by permission of the department of medicine of the University of Chicago.

The procedure was as follows. The patient appeared (from home or from the hospital) in the metabolism laboratory without breakfast and without a bath. After being weighed (in cotton gown) and measured, the patient rested in bed for one-half hour. Toward the end of this period of rest the temperature was taken and the pulse was counted for one minute. Two determinations of oxygen consumption were performed with the Benedict closed circuit apparatus modified with the Sanborn motor blower. At the end of the second determination, without disturbing the patient, the blood pressure was measured two or three times with a mercury sphygmomanometer and an average value was recorded.

PROCEDURE OF STATISTICAL ANALYSIS

From the outset, men and women were treated separately. The original plan included the treatment of seven variables. These variables were basal metabolic rate, pulse rate, respiration rate, body temperature, systolic blood pressure, diastolic blood pressure and age. It was found by experimental tabulations that pulse pressure bore a higher correlation with basal metabolism than did either systolic blood pressure or diastolic

blood pressure Pulse pressure was therefore substituted for these two measures Preliminary tabulations also revealed the absence of any relation between age and basal metabolic rate or age and pulse rate, and the relations between age and respiration rate, age and body temperature, and age and pulse pressure were of such low degree that it was decided to ignore them and eliminate age as a variable The number of variables was thus reduced to five

TABLE 1—*Interrelation of Basal Metabolic Rate, Pulse Rate, Pulse Pressure, Respiration Rate and Body Temperature*

Correlation of	846 Men	2,408 Women
Basal metabolic rate and pulse rate	$r_{12} = 0.525 \pm 0.017$	$r_{12} = 0.504 \pm 0.010$
Basal metabolic rate and pulse pressure	$r_{13} = 0.507 \pm 0.018$	$r_{13} = 0.448 \pm 0.011$
Basal metabolic rate and respiration rate	$r_{14} = 0.281 \pm 0.021$	$r_{14} = 0.308 \pm 0.012$
Basal metabolic rate and body temperature	$r_{15} = 0.233 \pm 0.022$	$r_{15} = 0.178 \pm 0.013$
Pulse rate and pulse pressure	$r_{23} = 0.394 \pm 0.020$	$r_{23} = 0.268 \pm 0.013$
Pulse rate and respiration rate	$r_{24} = 0.254 \pm 0.022$	$r_{24} = 0.219 \pm 0.013$
Pulse rate and body temperature	$r_{25} = 0.262 \pm 0.022$	$r_{25} = 0.289 \pm 0.012$
Pulse pressure and respiration rate	$r_{34} = 0.206 \pm 0.022$	$r_{34} = 0.184 \pm 0.013$
Pulse pressure and body temperature	$r_{35} = 0.154 \pm 0.023$	$r_{35} = 0.145 \pm 0.013$
Respiration rate and body temperature	$r_{45} = 0.048 \pm 0.023$	$r_{45} = 0.073 \pm 0.013$

TABLE 2—*Mean Value of Basal Metabolic Rate, Pulse Rate, Pulse Pressure, Respiration Rate and Body Temperature*

Variable	Mean Value of Each Variable	
	Men	Women
1 Basal metabolic rate	$-3.2\% \pm 0.63$	$-2.8\% \pm 0.34$
2 Pulse rate	73.3 ± 0.45	81.3 ± 0.28
3 Pulse pressure	43.9 ± 0.51	44.3 ± 0.31
4 Respiration rate	14.03 ± 0.14	14.68 ± 0.08
5 Body temperature	$97.7^{\circ} \pm 0.02$	$98.1^{\circ} \pm 0.01$

TABLE 3—*Standard Deviation of Basal Metabolic Rate, Pulse Rate, Pulse Pressure, Respiration Rate and Body Rate*

Variable	Standard Deviation of Each Variable	
	Men	Women
1 Basal metabolic rate	$18.3\% \pm 0.44$	$16.7\% \pm 0.24$
2 Pulse rate	13.2 ± 0.32	13.9 ± 0.20
3 Pulse pressure	14.9 ± 0.36	15.3 ± 0.22
4 Respiration rate	4.16 ± 0.10	4.12 ± 0.06
5 Body temperature (Fahrenheit)	$0.66^{\circ} \pm 0.02$	$0.61^{\circ} \pm 0.01$

The first step in the analysis was to prepare correlation sheets and calculate correlation coefficients for each of the ten interrelations of these measures The results of this treatment are contained in tables 1, 2 and 3 Correlation coefficients of basal metabolism with pulse rate and pulse pressure are not so large as those obtained by Read, but are practically identical with the findings of Minot and Means

Read obtained from 600 basal tests on both men and women a correlation between basal metabolic rate and pulse rate of 0.745

± 0.013 and between basal metabolic rate and pulse pressure of 0.625 ± 0.015 . Minot and Means³ found a correlation of 0.525 ± 0.036 between basal metabolism and pulse rate in the case of 180 observations on 126 patients with hyperthyroidism and a coefficient of 0.544 ± 0.044 in the case of 110 observations on 71 patients with leukemia. Sturgis and Tompkins⁴ and James Smith⁵ have published scatter diagrams of the relation between pulse rate and basal metabolism. Davies, Meakins and Sands⁶ have published a scatter diagram of basal metabolic rate and minute volume of cardiac output. These tables all show a pronounced relationship. The authors have not calculated correlation coefficients.

The fact that a lower correlation coefficient was obtained with the data here presented than that of Read is to be ascribed largely to the fact that the material of Read contained proportionately fewer cases within the normal range and more outside of it. Such a widening of the range would, of course, result in a higher correlation coefficient.

The next step in the analysis of the data here presented consisted in the application of multiple correlation technique to determine the best weighting of a regression equation for basal metabolism. Table 4 contains the multiple correlation coefficients of basal metabolism with pulse rate and pulse pressure and of basal metabolism with pulse rate, pulse pressure and respiration rate, together with the probable error of prediction for each. It becomes evident that the increase in prediction accuracy to be gained by the inclusion of body temperature as a fourth factor will be insignificant. Indeed, the gain in prediction accuracy from the inclusion of respiration rate in the prediction is inadequate to justify the added complexity its inclusion brings.

The regression equation for the prediction of the basal metabolism of men from their basal pulse rate and basal pulse pressure, as derived from this material, is $0.534 \text{ pulse rate} + 0.436 \text{ pulse pressure} - 62.55$. That for women is $0.497 \text{ pulse rate} + 0.368 \text{ pulse pressure} - 59.51$. These two formulas form an interesting comparison to the equation of Read, which is $0.75 \text{ pulse rate} + 0.57 \text{ pulse pressure} - 72$. All the formulas give about the same proportionate weight to pulse rate and pulse pressure.

3 Minot, G. R., and Means, J. H. The Metabolism-Pulse Ratio in Exophthalmic Goiter and in Leukemia, *Arch. Int. Med.* **33**: 576 (May) 1924.

4 Sturgis, C. C., and Tompkins, E. H. A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch. Int. Med.* **24**: 467 (Oct.) 1920.

5 Smith, J. H. Basal Metabolism. I. Correlation of Basal Metabolic Rate and Basal Pulse Rate, *Arch. Int. Med.* **41**: 663 (May) 1928.

6 Davies, H. W., Meakins, J., and Sands, J. The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood. V. The Blood Gases and Circulation Rate in Hyperthyroidism, *Heart* **11**: 299, 1924.

Certain sources of error should be considered in evaluating the foregoing procedures. In the first place, the lower of two rates has uniformly been selected as the true basal rate. As there has been no similar selection of the lower of two pulse complexes, this does not seem a justified procedure. The mean difference between the lower and the higher of two rates taken in succession during the same metabolism period is 5.29 per cent in the case of the men and 4.17 per cent in the case of the women. If one-half this correction is added to the foregoing prediction formulas to give the best prediction of midbasal rate, the formulas become

$$\begin{array}{l} 0.534 \text{ pulse rate} + 0.436 \text{ pulse pressure} - 59.94 \\ \text{and} \\ 0.497 \text{ pulse rate} + 0.368 \text{ pulse pressure} - 57.42 \end{array}$$

Random errors in the determination (or variation within the given period) of any variable entering into the formula would reduce the correlation. The degree of random error in the determination of basal metabolism becomes evident from an analysis of the cases of 291 men and 765 women on whom both basal rates were tabulated. The reliability of the method is 0.922 ± 0.006 in the case of the men and 0.940 ± 0.003 in the case of the women. If Spearman's formula for correction of the attenuation of basal metabolism is applied, the multiple coefficient of correlation of basal metabolism with pulse rate and pulse pressure is raised from 0.598 to 0.613 in the case of the men, while that of the women rises from 0.600 to 0.619. It is evident that error in the determination of basal metabolism exerts no significant influence over the relation as here described. It is not possible from the available data to determine the degree of influence of the error in the determination of pulse rate or pulse pressure, nor would it be theoretically permissible to correct for the attenuation of these measures if this could be done, since the error of these measurements must inevitably enter into any use that is made of them. The error in the determination of pulse rate may be expected to be low. That in the determination of pulse pressure is probably considerable.

Inspection of table 1 may already have called to the attention of the reader the fact that most of the variables correlate with basal metabolism more highly than with any other variable. This introduces the question of whether the intercorrelations of pulse rate, pulse pressure, respiration rate and body temperature with each other are due simply to the fact that each is correlated with basal metabolism. Is the association of rapid respiration and rapid pulse simply a reflection of the fact that both are commonly associated with an elevated basal metabolism, or does the pulse per se exert some influence over the respiration or vice versa? This question may be answered by observing the partial

correlation coefficients of pulse rate, pulse pressure, respiration rate, and body temperature with basal metabolism constant. These coefficients are tabulated in table 5.

A survey of table 5 will reveal that these partial coefficients of correlation are all low, but with one exception are all positive. The conclusion indicated seems to be that most, but not all, of the intercorrelation of pulse rate, pulse pressure, respiration rate and body temperature is due to the correlation of each of these measures with basal metabolism.

It may further be stated that this material indicates that rise of 1 degree Fahrenheit is equal to a rise in basal rate of 7 per cent in the case of men or 5 per cent in the case of the women. One degree centi-

TABLE 4—*Multiple Correlation Coefficients for Prediction of Basal Metabolic Rate*

	Multiple Correlation Coefficient	Probable Error of Prediction of Basal Rate
Men		
Basal metabolic rate with pulse rate and pulse pressure	$r_{1\ 23} = 0.508$	9.90%
Basal metabolic rate with pulse rate, pulse pressure and respiration rate	$r_{1\ 234} = 0.629$	9.59%
Women		
Basal metabolic rate with pulse rate and pulse pressure	$r_{1\ 23} = 0.600$	9.01%
Basal metabolic rate with pulse rate, pulse pressure and respiration rate	$r_{1\ 234} = 0.621$	8.83%

TABLE 5—*Partial Intercorrelation Coefficients with Basal Metabolic Rate Constant*

Partial Correlation of	Men	Women
Pulse rate and pulse pressure	$r_{23\ 1} = 0.175$	$r_{23\ 1} = 0.054$
Pulse rate and respiration rate	$r_{24\ 1} = 0.130$	$r_{24\ 1} = 0.078$
Pulse rate and body temperature	$r_{25\ 1} = 0.166$	$r_{25\ 1} = 0.269$
Pulse pressure and respiration rate	$r_{34\ 1} = 0.075$	$r_{34\ 1} = 0.085$
Pulse pressure and body temperature	$r_{35\ 1} = 0.041$	$r_{35\ 1} = 0.074$
Respiration rate and body temperature	$r_{45\ 1} = -0.019$	$r_{45\ 1} = 0.019$

grade is the equivalent of 12 per cent for the women and of 9 per cent for the men. These figures agree fairly well with those of DuBois⁷ (7.2 per cent for each degree Fahrenheit, 13 per cent for each degree centigrade).

THE VALUE OF BASAL PULSE COMPLEX

For an experimental trial of the three formulas, a retabulation was made of the basal metabolism determinations on 55 men and 120 women. These determinations were selected to secure a wide spread of basal rates and included only cases in which two successive basal rates differed by less than 5 per cent. The correlation of the lower basal rate with each of the formulas and with pulse rate \times pulse pressure is given in

⁷ DuBois, E. T. *Basal Metabolism in Health and Disease*, ed. 2, Philadelphia, Lea & Febiger, 1927, p. 389.

table 8 A scatter diagram of the agreement of basal pulse complex with basal rate is given in chart 1 It will be noted that 15 of 18 women having a basal pulse complex of $+15$ per cent or more have a basal rate of $+15$ per cent or more, and two of the remaining 3 have a basal rate of $+10$ per cent $+14$ per cent Four of 5 women having a pulse complex of -15 per cent or less also have a basal rate of -15 per cent or less This indicates a high degree of validity for the basal pulse complex in the diagnosis of disorders of metabolism

Despite the circular reasoning involved in the use of a measure developed from its agreement with basal metabolism as a check on

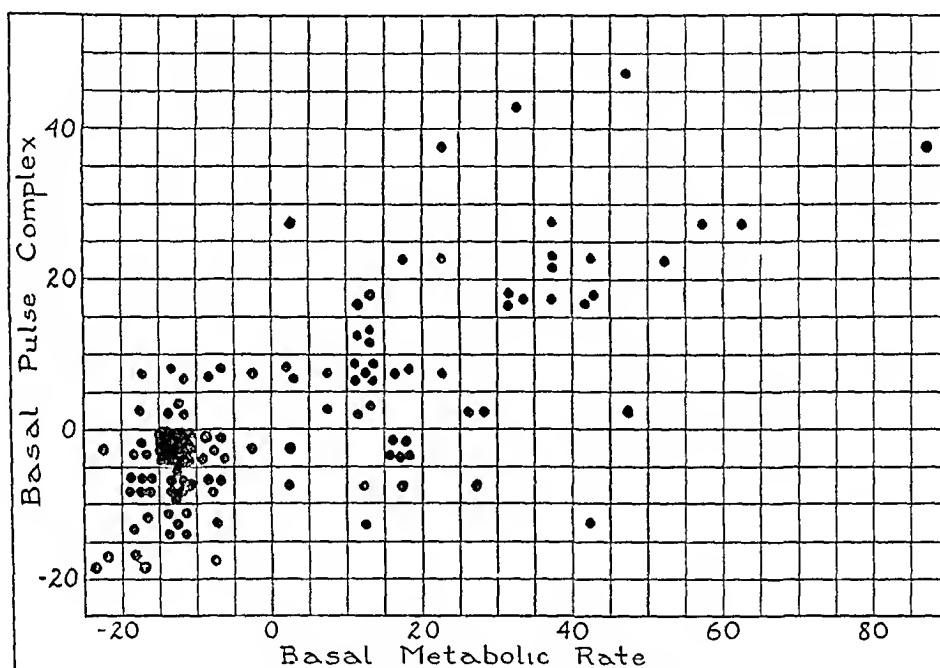


Chart 1—Scatter diagram showing agreement of basal pulse complex with basal rate

basal metabolism determinations, I am of the opinion that there is a definite place in clinical diagnosis for the use of such a measure as the prediction formula of Read or the basal pulse complex devised here. The importance of pulse rate and pulse pressure in the diagnosis of thyrotoxicosis and of myxedema is generally recognized. The value of these should be decidedly increased if rule of thumb methods are abandoned in favor of determination of basal pulse rate and basal pulse pressure and satisfactory formulas are applied.

It should be recognized that such a formula cannot be regarded as a substitute for basal metabolism determination, unless under conditions in which the latter cannot be secured. It should be recognized that basal pulse complex is not to be given equal clinical weight with basal metabolism. Nevertheless, as a confirmatory measure, particularly in the

diagnosis of doubtful cases, and in following the course of disease, it recommends itself to serious consideration. Chart 2 illustrates the course of basal metabolism and basal pulse complex in a patient with thyroid disease. This patient was treated with compound solution of

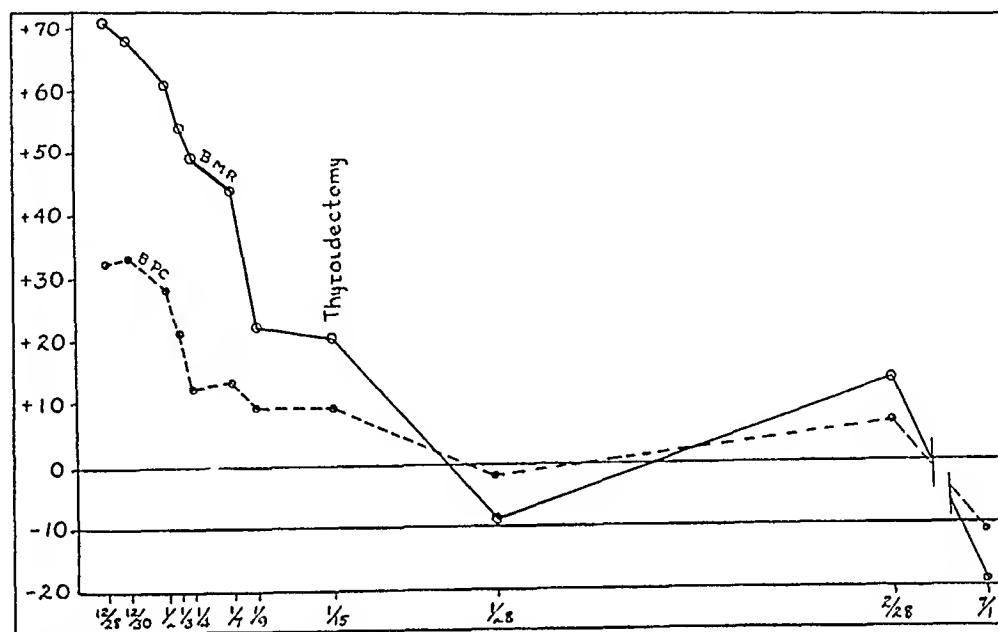


Chart 2—Course of basal metabolism and basal pulse complex in a man with diffuse hyperplastic goiter with severe hyperthyroidism

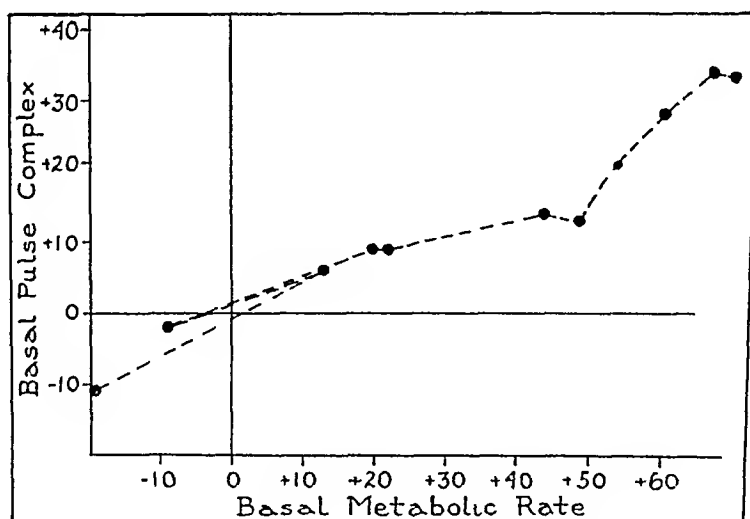


Chart 3—Basal pulse complex plotted against basal metabolic rate in the case of a man with diffuse hyperplastic goiter with severe hyperthyroidism

iodine and subjected to thyroidectomy with good results. It will be observed that while basal pulse complex does not deviate as far in either direction in this extreme case as basal metabolic rate, yet the parallelism of the two is almost perfect. This is perhaps more clearly demonstrated in chart 3. In chart 3 the line of dots approaches a straight line, indi-

TABLE 6—Basal Pulse Complex in Men

Pulse Pressure	Pulse Rate															
	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115
15	-32	-29	-27	-24	-21	-19	-16	-13	-11	-8	-5	-3	0	+3	+5	+8
20	-30	-27	-25	-22	-19	-17	-14	-11	-9	-6	-3	+2	+4	+5	+8	+10
25	-28	-25	-23	-20	-17	-15	-12	-9	-6	-4	-1	+2	+4	+7	+10	+12
30	-26	-23	-20	-17	-13	-10	-7	-5	-2	-1	+3	+6	+9	+11	+14	+17
35	-23	-21	-18	-15	-13	-10	-8	-5	-2	+3	+6	+8	+11	+14	+16	+19
40	-21	-18	-16	-13	-10	-8	-5	-2	+2	+5	+7	+10	+13	+16	+18	+21
45	-19	-16	-14	-11	-9	-6	-3	+2	+5	+7	+10	+13	+15	+18	+21	+23
50	-17	-14	-11	-9	-7	-4	-1	+4	+7	+9	+12	+15	+17	+20	+23	+25
55	-15	-12	-9	-7	-4	-1	+1	+6	+9	+12	+15	+17	+20	+22	+25	+28
60	-12	-10	-7	-4	-2	0	+3	+8	+11	+14	+16	+19	+22	+24	+27	+30
65	-10	-7	-5	-2	0	+3	+6	+11	+13	+16	+19	+21	+24	+27	+29	+32
70	-8	-5	-3	0	+2	+5	+8	+11	+15	+18	+21	+23	+26	+29	+32	+35
75	-6	-3	0	+2	+4	+7	+10	+13	+15	+18	+21	+23	+26	+29	+32	+35
80	-4	-1	+2	+4	+7	+10	+12	+15	+18	+20	+23	+25	+28	+31	+34	+36
85	-1	+1	+4	+7	+9	+12	+15	+17	+20	+23	+25	+28	+31	+33	+36	+39
90	+1	+4	+6	+9	+11	+14	+17	+19	+22	+25	+27	+30	+33	+35	+38	+41
95	+3	+6	+8	+11	+13	+16	+19	+22	+24	+27	+30	+32	+35	+38	+40	+43
100	+5	+7	+10	+13	+15	+18	+21	+24	+26	+29	+32	+34	+37	+40	+42	+45
105	+7	+9	+12	+15	+18	+21	+24	+27	+29	+32	+34	+37	+40	+42	+45	+48
110	+9	+12	+15	+18	+20	+23	+26	+29	+31	+34	+36	+39	+41	+44	+47	+50
115	+12	+15	+17	+20	+22	+25	+28	+30	+33	+36	+38	+41	+44	+46	+49	+51
120	+14	+17	+19	+22	+24	+27	+30	+32	+35	+38	+40	+43	+45	+48	+51	+53

TABLE 7—Basal Pulse Complex in Women

Pulse Pressure	Pulse Rate															
	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115
15	-32	-30	-27	-25	-22	-20	-17	-15	-12	-10	-7	-5	-2	0	+3	+5
20	-30	-28	-25	-23	-20	-18	-15	-13	-10	-8	-5	-3	-1	+2	+5	+7
25	-28	-26	-23	-21	-18	-16	-13	-11	-8	-6	-3	-1	+1	+4	+6	+9
30	-27	-24	-22	-20	-17	-15	-12	-9	-7	-4	-2	+1	+3	+6	+8	+11
35	-25	-22	-20	-17	-15	-12	-10	-7	-5	-2	0	+3	+5	+8	+10	+13
40	-23	-20	-18	-15	-13	-10	-8	-5	-3	0	+2	+4	+7	+9	+12	+14
45	-21	-19	-16	-14	-11	-9	-6	-4	-1	+3	+6	+8	+10	+11	+14	+16
50	-19	-17	-14	-12	-10	-7	-4	-2	+1	+5	+8	+10	+13	+15	+17	+19
55	-17	-15	-12	-10	-8	-5	-2	+3	+6	+9	+11	+14	+16	+18	+21	+23
60	-15	-13	-10	-8	-6	-3	-1	+4	+7	+10	+12	+15	+17	+20	+23	+25
65	-14	-11	-9	-6	-4	-1	+3	+6	+9	+11	+14	+16	+19	+22	+25	+27
70	-12	-9	-7	-5	-2	+1	+5	+8	+10	+12	+15	+17	+20	+23	+26	+29
75	-10	-7	-5	-3	0	+2	+6	+9	+11	+14	+16	+19	+22	+25	+28	+31
80	-8	-6	-4	-2	+1	+4	+7	+9	+12	+14	+17	+19	+22	+25	+29	+32
85	-6	-4	-2	+1	+4	+7	+9	+11	+14	+16	+19	+21	+24	+27	+30	+33
90	-5	-3	0	+2	+5	+8	+10	+13	+15	+18	+20	+23	+25	+28	+31	+34
95	-3	-1	+2	+4	+7	+9	+12	+15	+17	+20	+22	+25	+27	+30	+33	+36
100	-1	+2	+4	+7	+9	+11	+14	+17	+19	+22	+24	+27	+29	+32	+35	+38
105	+1	+3	+6	+8	+10	+13	+16	+18	+21	+24	+26	+29	+31	+34	+37	+40
110	+3	+5	+8	+10	+13	+15	+18	+20	+23	+25	+28	+30	+33	+36	+39	+42
115	+5	+7	+10	+12	+15	+17	+20	+22	+25	+27	+30	+32	+35	+38	+41	+44
120	+7	+9	+12	+14	+17	+19	+22	+24	+27	+29	+32	+34	+37	+40	+43	+46

cating a very close correspondence between basal rate and basal pulse complex. Chart 3 suggests that basal pulse complex gains greater validity as an individualized measure for following a particular patient.

Read's formula gives a prediction that is typically about 10 per cent higher than the basal pulse complex of normal subjects. This difference is perhaps associated with the low level of metabolism obtained in the metabolism laboratories at the University of Chicago. Read's formula also tends to emphasize deviation more than the basal pulse complex. All that I am able to state regarding the relative merits of the two are that the basal pulse complex is based on a much larger series and fits that series better than Read's formula. It is possible that it will be somewhat low or somewhat high for other laboratories.

Tables 6 and 7 are conveniently arranged for the determination of basal pulse complex. After locating the pulse rate column and the pulse pressure row, one directly reads off the basal pulse complex at the junc-

TABLE 8—*Correlation of Various Prediction Formulas with Basal Rate (One Hundred and Twenty Women)*

Basal pulse complex with basal rate	$r = 0.73 \pm 0.029$
Read's formula with basal rate	$r = 0.64 \pm 0.036$
Pulse rate \times pulse pressure with basal rate	$r = 0.68 \pm 0.033$
	Mean Standard Deviation
Basal metabolic rate	+ 4.28% 22.1%
Basal pulse complex	+ 3.04% 13.1%
Read's formula	+17.38% 20.4%
Pulse rate \times pulse pressure	-41.0 22.1

tion of the two. With these tables, 62 basal pulse complex determinations were made on 14 apparently normal university freshmen. The mean value obtained was -13 per cent and the standard deviation 6.77 per cent (probable error = ± 4.56 per cent). This mean seems very low, but one must remember that the mean basal metabolic rate simultaneously taken for this series was -5.5 per cent and the standard deviation was 9.2 per cent (probable error = ± 6.2 per cent). The difference in the two means is 7.5 per cent. This may be in part accounted for by the fact that the series is very short, and the size of the standard deviation of basal metabolic rate suggests that the sampling is erratic. A second possible contributing factor is the fact that in these cases the pulse was taken during the actual test, while in the clinic series it was taken toward the end of the half hour rest period. Probably the most important factor, however, is that in the clinic series the portion of persons with a slight tachycardia of nervous origin is almost certainly higher than in normal freshmen, since it is these cases that excite the suspicion of hyperthyroidism. For differential diagnosis of such cases a formula based on clinic material in which they are well represented should be of greater value than one based on a truly normal population.

It should be noted in closing that if basal pulse complex is compared with any other basal metabolism standard than the Aub-DuBois, allowance for difference in the level of the metabolism standards should be made in a manner previously outlined⁸

CONCLUSIONS

Formulas and tables are here presented for the calculation of a basal pulse complex which is comparable with the basal metabolism of adults

This measure should be of value as a procedure supplementary and confirmatory to basal metabolism determination in the diagnosis of metabolic disease

⁸ Jenkins, R. L. Basal Metabolism I The Error of Basal Metabolism Determination and the Normal Range of Basal Metabolism, Arch Int Med, this issue, p 181

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

IV THE EFFECT ON BASAL METABOLISM OF THE DAILY ADMINISTRATION OF ABOUT 0.75 MG OF IODINE *

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AND

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We have previously shown that in Boston the daily administration of about 6 mg of iodine in the form of the compound solution produces a maximum reduction in basal metabolism in most hospital patients with exophthalmic goiter,¹ and that the daily administration of about 3 mg produces on the average only half as much reduction² and the daily administration of about 1.5 mg on the average only one-third as much reduction³. As a continuation of our study of the range of effective iodine dosage in exophthalmic goiter we have now investigated the effect of the daily administration of about 0.75 mg of iodine in twelve unselected hospital patients with the disease.

METHOD AND RESULTS

Method—The same routine was followed as with the hospital patients in the first paper of this series,¹ except that 1 drop of a 12.5 per

* Submitted for publication, April 21, 1931

From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital, Boston. This paper was written after the first two authors had started work at the Rush Medical College and the Presbyterian Hospital, Chicago.

1 Thompson, W O, Braley, A G, Thompson, P K, and Thorp, E G. The Range of Effective Iodine Dosage in Exophthalmic Goiter. I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, *Arch Int Med* **45** 261 (Feb) 1930.

2 Thompson, W O, Thorp, E G, Thompson, P K, and Cohen, A C. The Range of Effective Iodine Dosage in Exophthalmic Goiter. II. The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, *Arch Int Med* **45** 420 (March) 1930.

3 Thompson, W O, Cohen, A C, Thompson, P K, Thorp, E G, and Braley, A G. The Range of Effective Iodine Dosage in Exophthalmic Goiter. III. The Effect on Basal Metabolism of the Daily Administration of One-Quarter Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, *Arch Int Med* **45** 430 (March) 1930.

TABLE 1—Summary of the Consecutive Effects of Rest, the Daily Administration in Hospital Patients

Patient	Laboratory Number	Age	Height, Cm	Admission			Rest					
				Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg	Change in Basal Metabolic Rate, Points	Number of Days Before Level Was Reached	Length of Time Effect Was Observed, Days
Mrs G H	1340	42	156	+69	107	52.9	+48	99	51.6	-21	1	3
Mr G C	6711	57	173	+38	115	58.9	+40	93	57.7	+2	0	4
Mrs L P	6723	23	160	+81	118	48.4	+64	100	45.5	-17	1	6
Mrs M M	6727	52	154	+56	102	43.7	+33	88	43.9	-23	1-2	7
Mr P G	6746	28	178	+47	120	49.3	+33	103	48.5	-14	1-3	6
Mr C F	6752	49	174	+40	104	59.4	+26	81	58.2	-14	4	6
Miss L L	6771	13	155	+57	103	34.5	+38	94	34.6	-19	1	6
Mr W T	6799	41	162	+53	112	43.1	+39	87	43.3	-14	1-2	6
Mrs E P	6885	22	162	+52	116	48.7	+36	105	49.0	-16	2	3
Mr A C	6894	26	171	+41	87	55.8	+31	73	54.0	-10	4	7
Mrs M G	6956	38	160	+65	128	52.9	+43	98	53.1	-22	1-2	4
Mr E B	6994	32	166	+40	76	49.6	+33	72	50.5	-7	1	4
Average all cases (12)				+53			+39			-15		5
Average all cases in which the basal metabolic rate dropped 10 points or more (4)				+51			+35			-16		6

TABLE 2—Detailed Presentation of Basal

Patient	Laboratory No	Days Before Starting Iodine																	
		9	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9
Irs G H †	1340					A	+69	+50	+47	+47	+49		+43	+43	+45	+42	+50	+58	
Ir G C	6711				A	+38		+42	+37	+40	+35		+32		+44	+27	+37	+36	+56
Irs L P ‖	6723	A		+81	+64				+72	+75	+74						+68	+56	+61
Irs M M	6727	A	+56		+31		+39	+26	+30	+37	+29	+44		+27	+32	+22	+27	+26	+36
Ir P G	6746			+47			+26	+28	+35	+30	+26	+21		+17	+22	+20	+14	+12	+17
Ir C F	6752		A	+40	+49	+35	+34	+22		+30	+29	+26	+25	+30	+23		+11	+17	+17
Miss L L	6771		A	+57	+37	+41	+43	+31		+39	+42	+33	+40	+40	+43		+39	+43	+42
Mr W T	6799		A	+53		+43	+43	+37		+41	+42	+38		+36	+33		+25	+28	+26
Mrs E P	6885				A		+52	+42	+35	+36	+38	+39		+38	+28	+28	+35	+35	+34†
Mr A C	6894	A	+41		+37	+35	+30		+31	+32		+33	+23	+23	+30	+28	+26		+24
Mrs M G	6956					+65		+44	+43	+43	+41		+29	+33	+35	+37	+35	+29	
Mr E B	6994				A	+40	+30	+35	+35	+31		+39	+40	+37	+27	+36	+40		+33

* A indicates admission to the hospital, S, subtotal thyroidectomy, LH, left hemithyroidectomy

† A right hemithyroidectomy had been performed for exophthalmic goiter seven years before present admission

‡ The time when larger doses (30 minims daily) were started

*of 0.75 Mg of Iodine and of Much Larger Doses Given Immediately Afterward
with Exophthalmic Goiter*

During Administration of 0.75 Mg of Iodine Daily, in the Form of Compound Solution								During Daily Administration of Larger Doses							
Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg	Change in Basal Meta- bolic Rate, Points	Length of Time Effect Was Observed, Days	Time the Drop Began, Days	Drop in Basal Metabolic Rate in First 24 Hours, Points	Time Required for Maxi- mum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg	Change in Basal Meta- bolic Rate, Points	Length of Time Effect Was Observed, Days	Size of Dose, Minims	Total Change in Basal Metabolic Rate on All Doses	Estimated Weight of Thyroid Gland at Time of Operation, Gm
+60	100	50.5	+12	15	0	0	0	+33	82	55.4	-27	16	30	-15	46
+48	95	53.6	+8	13	0	0	0	+15	77	52.9	-33	13	30	-25	
+60	117	41.2	-4	13	0	0	0	+14	74	41.1	-46	12	30	-50	
+29	73	45.7	-4	11	0	0	0	+19	70	45.5	-10	3	30	-14	34
+14	91	48.2	-19	11	2	0	4-7	+7	88	49.0	-7	9	30	-26	40
+15	82	55.8	-11	10	7	0	7	+4	76	57.0	-11	9	30	-22	27
+39	95	35.7	+1	10	0	0	0	+16	79	39.7	-23	15	30	-22	39
+26	81	43.9	-13	10	6-7	0	6-7	+13	76	45.3	-13	12	30	-26	
+32	96	49.6	-4	9	0	0	0	+19	88	51.2	-13	10	30	-17	61
+26	72	53.8	-5	10	0	0	0	+18	74	53.3	-8	10	30	-13	54
+31	93	54.7	-12	12	2-3	0	2-3	+31	94	58.2	0	12	30	-12	
+36	82	49.2	+3	10	0	0	0	+13	70	50.8	-23	10	30	-20	76
+35			-4	11				+17			-18	11		-22	
+22			-13	11				+14			-8	11		-21	

Metabolism Data Summarized in Table 1'

Days After Starting Iodine																			
10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
+54	+65	+68	+57		+57†		+53	+52	+45	+43	+35	+32		+30	+29	+36	+39	+32	+31
+45		+49	+42†	+48	+46	+35	+30		+34	+23	+12	+13	+16	+19		+13 S			
+59	+57		+64†	+47	+53	+47	+42	+41		+28	+24	+23	+17	+12	+14 S				
	+28†	+31	+21	+19	S														
	+11†	+12	+10	+9	+8	+8		+8	+1	+8 S									
+15†	+20	+8		±0	+7	+10	+2	+3	+6 S										
+32†	+37	+35		+32	+36	+28	+28	+24	+24		+23	+16	+15	+17	+36 S				
+25†	+26	+23		+20	+31	+10	+17	+8	+13			+18 S							
	+38	+28	+34	+24	+22	+22		+8	+20 S										
+24†	+29	+30	+28	+25		+18	+19	+18	+19	+14	S								
+31	+32	+31†	+30	+33	+31		+29	+27	+28	+34	+32	+35	+49#S						
+36†	+51	+41	+39	+41		+28	+23	+13	+12	+15	S								

‡ The patient suffered from acute tonsillitis with fever from the fourth day before starting iodine until the fifth day afterward

The patient worried about the operation

cent compound solution of iodine (about 0.75 mg of iodine)⁴ was administered daily in the metabolism laboratory instead of 1 drop of the undiluted solution. It should be emphasized that the administration of iodine was not begun until the basal metabolism had reached a stationary level during rest.

Results—The data are recorded in tables 1 and 2. It may be seen that four of the twelve patients at rest in bed showed a reduction in basal metabolism of from 11 to 19 points during the daily administration of about 0.75 mg of iodine in the form of the compound solution, six showed no change, and two showed an increase. The average basal metabolic rate shortly after admission was plus 53 per cent, after a period of rest, it was plus 39 per cent, after reaching a level during the daily administration of about 0.75 mg of iodine, it was plus 35 per cent, and on larger doses administered immediately afterward, it was plus 17 per cent. The corresponding figures for the four cases in which the basal metabolic rate dropped 10 or more points were plus 51, plus 35, plus 22 and plus 14 per cent, respectively (table 1).

It is of some interest that the drop in basal metabolism from rest in bed alone was almost exactly the same in all four series of hospital patients (the 6 mg,¹ 3 mg,² 1.5 mg³ and 0.75 mg series).

Various types of response to the administration of 0.75 mg daily are recorded in charts 1 to 6.

Time Required for Maximum Reduction in Basal Metabolism—In the four patients who showed a reduction of more than 10 points, the maximum drop occurred in from two to seven days (from five to six days on the average). The average daily drop in basal metabolism in these four patients was from 2.3 to 2.8 points. In the nine patients who showed a reduction in basal metabolism of 10 or more points during the administration of large doses immediately after the small dose, the lowest level appeared in from three to twelve days, or in an average of seven days from the time the large dose was started, i. e., in the same time that is required for the basal metabolism to drop to its lowest level when large doses are given initially.

COMPARISON OF EFFECTS OF THE VARIOUS DOSES OF IODINE USED IN THE FOUR SERIES OF HOSPITAL PATIENTS

In charts 7 and 8 and in table 3 we have compared the effects on basal metabolism of administering about 6 mg,¹ 3 mg,² 1.5 mg³ and 0.75 mg of iodine daily to four series of hospital patients. The per-

⁴ Owing to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of a 12.5 per cent compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle.

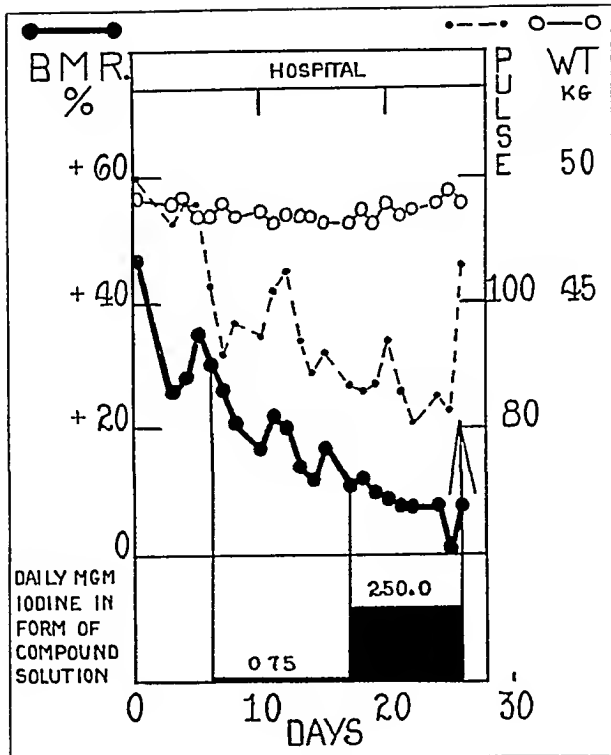


Fig 1 (Mr P G, lab no 6746) —The greatest reduction in basal metabolism observed during the daily administration of 0.75 mg of iodine. In this and subsequent charts, the arrow denotes subtotal thyroidectomy

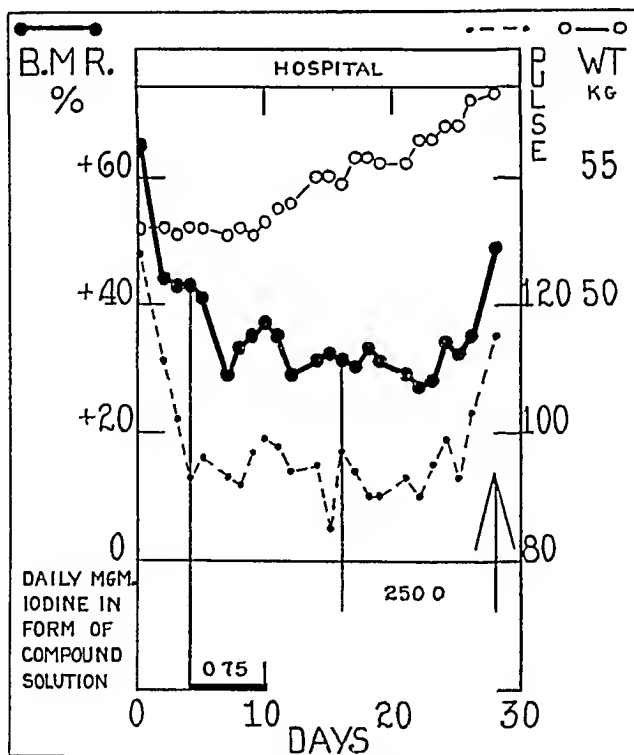


Fig 2 (Mrs M G, lab no 6956) —Slight reduction in the basal metabolic rate during the daily administration of 0.75 mg of iodine, and no further reduction during the immediate subsequent administration of much larger doses

centage approach toward the average normal level of metabolism that occurred during the daily administration of 3 mg, 1.5 mg and 0.75 mg is roughly seven-twelfths, four-twelfths and two-twelfths, respectively, of that which occurred during the daily administration of 6 mg (table 3), i. e., if the percentage approach toward normal be plotted against the daily dose of iodine, the points roughly fall on a straight line (chart 9)

From table 3 it may be seen that the 1.5 mg series is the only one in which the results were definite enough to say that the small dose interfered with the effect of the large dose given immediately afterward. This phenomenon was so consistent in this series that it seems to have

TABLE 3—*Comparison of the Effects on Basal Metabolism of the Daily Administration of About 6, 3, 1.5 and 0.75 mg of Iodine to Hospital Patients with Exophthalmic Goiter*

Number of Cases	Approximate Size of Small Dose, Mg of Iodine Daily	Average Basal Metabolic Rate, per Cent of Normal				During Administration of Small Dose		During Administration of All Doses	
		On Admission	After Reaching a Level During Rest	After Reaching a Level During Administration of Small Dose	After Reaching a Level During Administration of Large Dose	Average Drop in Basal Metabolic Rate, Points	Percentage Approach of Basal Metabolic Rate Toward Normal Level	Average Drop in Basal Metabolic Rate, Points	Percentage Approach of Basal Metabolic Rate Toward Normal Level
14*	6.00	+62	+48	+19	+21	29	60	27	56
20	3.00	+54	+40	+26	+21	14	35	19	48
14	1.50	+62	+43	+34	+29	9	20	14	33
12	0.75	+53	+39	+35	+17	4	10	22	56

* Three cases in which large doses were not given are not considered in this table. Their omission does not alter the figures for the small dose appreciably (Thompson, Brailey, Thompson and Thorp [footnote 1, table 1]).

been more than a coincidence. The data perhaps suggest that a similar phenomenon occurred in the 3 mg series² but this does not appear to have been the case in the 0.75 mg series. We are unable to offer any more satisfactory explanation for this difference than that already given in the third paper of this series,³ in which certain aspects of the effects of these four doses are compared in more detail.

COMMENT

The changes observed in the basal metabolism during the daily administration of 0.75 mg of iodine were so small that it is somewhat questionable whether they were caused by rest or by the iodine. However, since the metabolism did not drop in most cases during the daily administration of 0.75 mg it appears that in most instances we had either secured a maximum effect from rest before this dose was started, or else the daily administration of 0.75 mg prevented a further drop

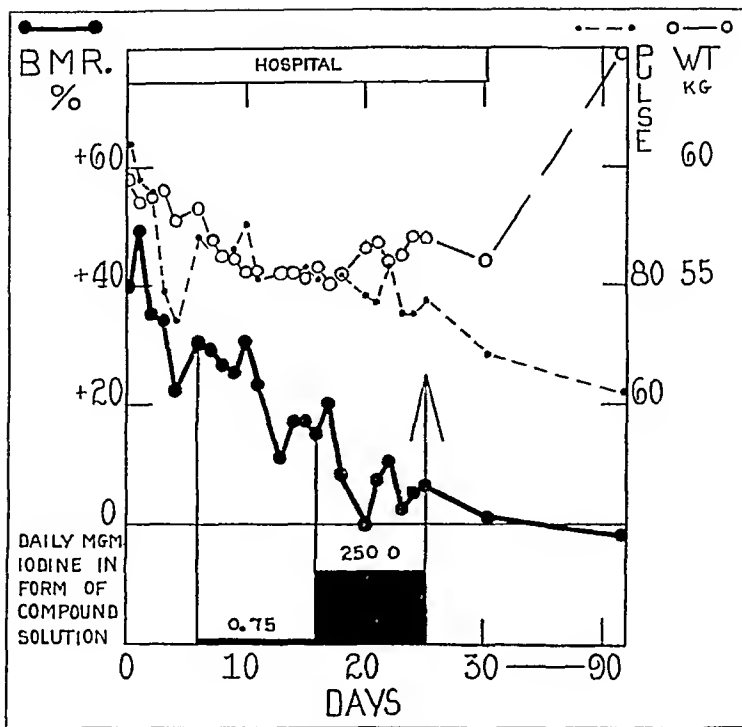


Fig 3 (Mr C F, lab no 6752) —Slight reduction in basal metabolic rate during the daily administration of 0.75 mg of iodine followed by a slight further reduction during the administration of much larger doses

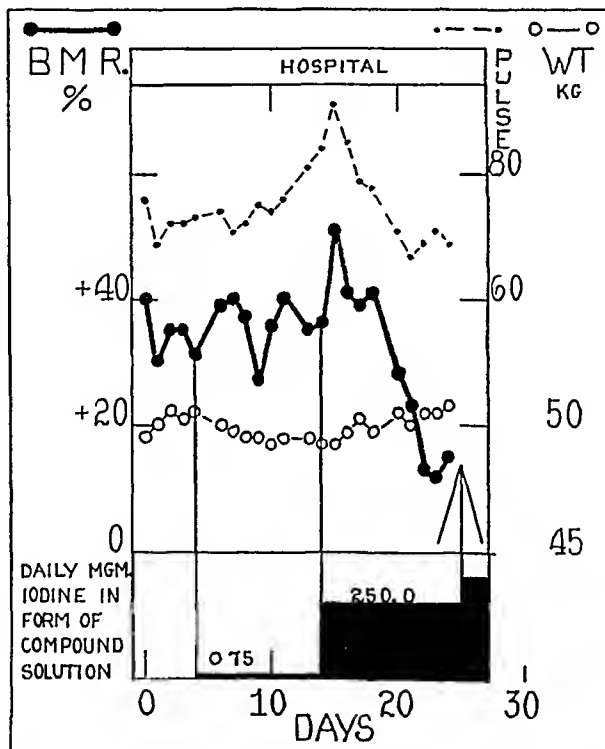


Fig 4 (Mr E B, lab no 6994) —No reduction in basal metabolic rate during the daily administration of 0.75 mg of iodine, followed by a well marked reduction during the administration of much larger doses

from rest alone. In any case, the response was so small in those that showed a reduction in basal metabolism on this dose that it is impossible with present methods to measure any slight reduction that might occasionally occur during the administration of a still smaller dose.

It may now be said that whereas the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston is about 6 mg daily, the smallest dose that will produce any reduction is a little greater than 0.75 mg per day in about two thirds of the cases, and is probably not very much less than 0.75 mg in the other third. Therefore, the range of effective iodine dosage in the majority of cases of exophthalmic goiter in Boston lies roughly between 0.75 and 6 mg per day. Since the average reduction of the seven cases of the 6 mg series that showed the smallest response⁵ is greater than the average for the seven of the 1.5 mg series that responded, and since the average reduction of the four cases of the 6 mg series that showed the smallest response is greater than the average for the four of the 0.75 mg series that responded, the minimum dose of iodine that will produce a maximum reduction in basal metabolism is probably rarely as low as 1.5 mg per day. It may occasionally be as low as this, however, in spite of the presence of a considerable amount of palpable thyroid tissue.⁶

While the minimum dose that will produce a maximum reduction in basal metabolism and the smallest dose that will produce any effect vary from case to case, it is uncertain whether one is usually large when the other is large and small when the other is small or whether the magnitude of the spread in effective dosage varies markedly from case to case. It is also uncertain what the greatest minimum dose is that is ever necessary to produce a maximum reduction in basal metabolism. It is sometimes greater than 6 mg daily.⁷ Moreover, we wish to stress once again that this dose is not recommended in the routine treatment for the disease.

THE WEIGHT OF THE THYROID GLAND

The data recorded in the first three papers of this series and summarized in the third paper³ suggested that the amount of iodine neces-

5 Throughout this study a response has arbitrarily been assumed to be a reduction of 10 or more points in the basal metabolic rate.

6 Thompson, Cohen, Thompson, Thorp and Braley (footnote 3, table 3, case 5272).

7 Thompson, Braley, Thompson and Thorp (footnote 1 charts 5, 6, 9 and 10) Thompson, W. O., and Thompson, P. K. Exophthalmic Goiter. The Development of Refractoriness to Iodine, *Arch. Int. Med.* 48:1 (Sept.) 1931, cases 4822 and 5168.

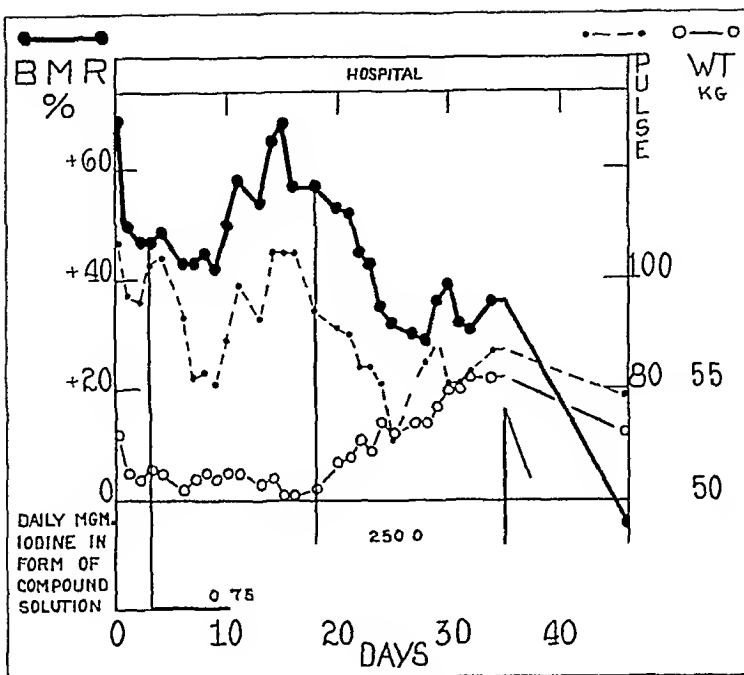


Fig 5 (Mrs G H, lab no 1340) —Increase in basal metabolic rate and in the severity of the signs and symptoms of exophthalmic goiter during the daily administration of 0.75 mg of iodine, followed by a decrease in both factors during the immediate subsequent administration of much larger doses

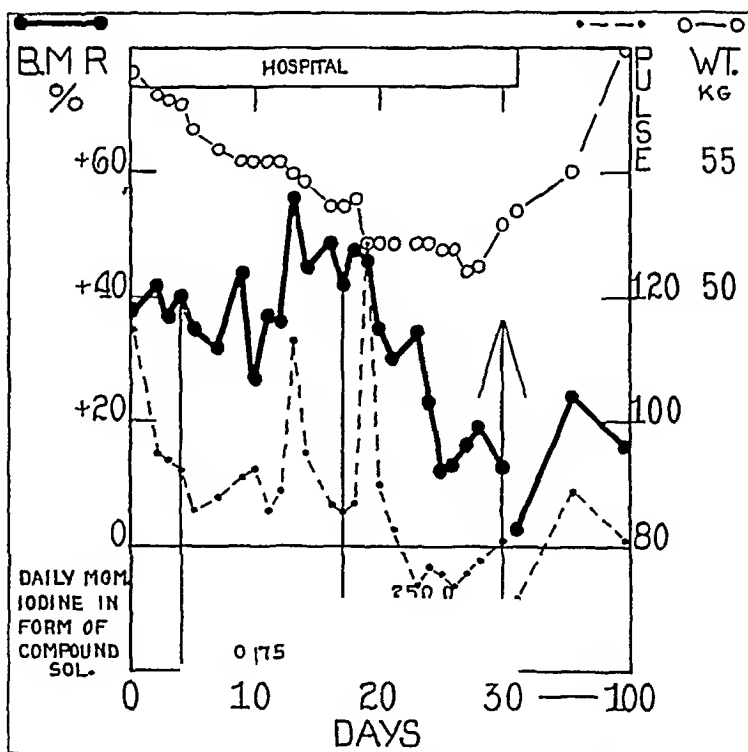


Fig 6 (Mr G C, lab no 6711) —A slight increase in the basal metabolic rate and in the severity of signs and symptoms of exophthalmic goiter during the daily administration of 0.75 mg of iodine, followed by a decrease in both factors during the immediate subsequent administration of much larger doses

sally to produce a maximum reduction in basal metabolism varied with the weight of the thyroid gland. The data in this paper perhaps serve to emphasize this point. The glands, on the whole, were not large, the average weight of those weighed being only 47 Gm., yet the average response in these particular cases was only 4 points (from plus 35 to plus 31 per cent). Using the same method of calculation as in the third paper of the series,³ these thyroid glands would have contained on the basis of the figures of Marine and Lenhart,⁸ about 11 mg. of iodine before medication was started and about 29 mg. after iodine was administered—a difference of 18 mg., on the basis of the figures from the Mayo Clinic (Wilson and Kendall⁹ and Weir¹⁰), about 9 and 24 mg., respectively—a difference of 15 mg., and on the basis of Cattell's¹¹ figures, about 20 and 40 mg., respectively—a difference of 20 mg. In the average time required for the response to 15 mg. daily to become maximum (i. e., from five to six days), not more than 45 mg. of iodine would have been supplied to the patients, a totally inadequate amount to cause a maximum storage of colloid. This perhaps explains not only the very slight average response, but also the small amount of reduction in basal metabolism in those who did respond. For convenience, table 6 of the third paper³ has been brought up to date in table 4.

A comparison of the amount of iodine available for the storage of colloid on the four doses used, with the effect of these doses on the basal metabolism, suggests a rough parallelism between the two (table 5 and chart 10). Thus it appears that the percentage approach of the basal metabolism toward the normal level, the daily dose of iodine within the limits of 0.75 and 6 mg. and the amount of iodine available for the storage of colloid on doses within these limits are roughly proportional to one another.

It was pointed out in the third paper³ that the slower rate of reduction in the basal metabolism during the daily administration of 15 and

8 Marine, D., and Lenhart, C. H. Pathological Anatomy of Exophthalmic Goiter. The Anatomical and Physiological Relations of the Thyroid Gland to the Disease, Treatment, Arch. Int. Med. **8** 265 (Sept.) 1911.

9 Wilson, L. B., and Kendall, E. C. The Relationship of the Pathological Histology and the Iodin Compounds of the Human Thyroid, Am. J. M. Sc. **178** 79, 1916.

10 Weir, J. F. The Thyroxin and Tryptophane Content of the Diseased Thyroid Gland, and the Iodin Compounds in Desiccated Thyroid, Am. J. M. Sc. **169** 860, 1925.

11 Cattell, R. B. The Pathology of Exophthalmic Goitre. A Histological and Chemical Study of the Changes Following the Administration of Iodin (Lugol's Solution), Boston M. & S. J. **192** 989, 1925.

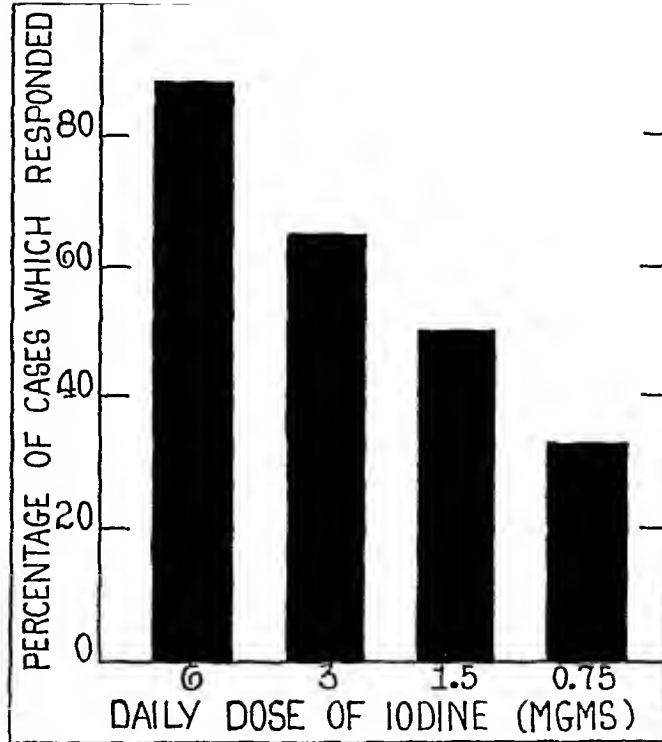


Fig 7—The percentage of patients who responded to each dose of iodine

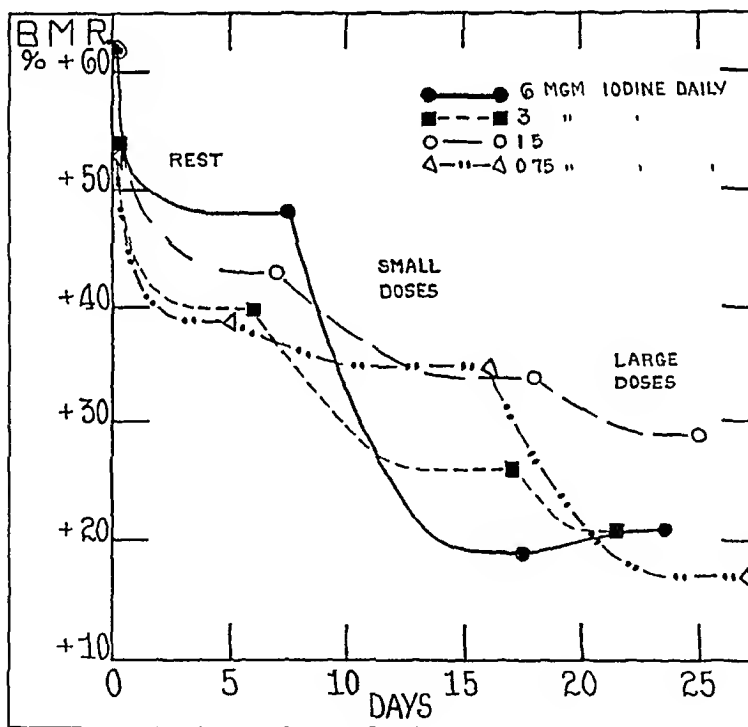


Fig 8—A comparison of the effects on basal metabolism of the daily administration of 6, 3, 1.5 and 0.75 mg of iodine, respectively, to four series of hospital patients. In each case the first point is the average of the basal metabolisms shortly after admission, the second point is the average of the levels to which the metabolism fell from rest alone, the third point is the average of the levels to which the metabolism fell during the administration of small doses, and the fourth point is the average of the levels during the immediate subsequent administration of larger doses (usually about 250 mg daily). Only those cases are considered in which the effect of larger doses was noted. The points are arbitrarily connected by curved lines, as these denote the true course of the basal metabolism more nearly than straight lines.

TABLE 4—Summary of Relationship Between the Estimated Iodine Capacity of the Thyroid and the Theoretical Amount of Iodine Available for Storage (of Colloid) by This Gland on the Various Doses Administered

Possible Iodine Content of Thyroid Glands in Our Series																
Number Cases	Average Weight of Thyroid Gland, Gm	Average Time Required for Maximum Reduction in Basal Metabolic Rate, Days	Amount of Iodine Administered for Each Case in Time Required	On Basis of Figures of Marine and Lenhart			On Basis of Mayo Clinic Figures			On Basis of Cattell's Figures			Average Basal Metabolic Rate, per Cent of Normal	Drop in Basal Metabolic Rate, Points		
				Before Iodine Administered	After Iodine Administered	Iodine in Gland Before Iodine Administered	Before Iodine Administered	After Iodine Administered	Iodine in Gland Before Iodine Administered	Before Iodine Administered	After Iodine Administered	Iodine in Gland Before Iodine Administered				
															Mg	Mg
8	111	7	42	25	68	67	21	57	63	17	93	89	+51	+18	33	
12	77	7	21	18	47	39	15	40	36	32	65	53	+39	+28	11	
8	49	6	18	11	30	29	9	25	27	21	41	39	+11	+18	23	
11	57	5	75	13	35	21	11	29	19	24	48	32	+42	+33	9	
5	51	4	60	12	33	18	10	28	16	23	45	29	+41	+24	17	
4	29	4	60	7	18	13	6	15	12	12	24	18	+40	+21	19	
1	200	1	12	46	123	47	38	113	39	84	168	85	+53	+39	14	
8	47	5-6	45	11	29	16	9	24	14	20	40	25	+35	+31	4	
2	33.5	6	45	8	21	13	6	17	11	14	28	19	+30	+15	15	

* All of these figures are probably less than those recorded because, during the period of observation, the gland may lose iodine in its secretion. The amount thus lost cannot be accurately estimated at present, but it probably is not large.

+ The three subdivisions of the 15 mg. data are made because, by including among those that responded to iodine, the one case (no. 6530) in which the thyroid weighed 154 Gm. and in which the metabolism dropped only 10 points on 15 mg. of iodine, the average weight of the thyroid in such cases is practically doubled (54 instead of 29 Gm.), and the difference between the iodine capacity of the gland and the theoretical amount of iodine available for storage (of colloid) is markedly increased.

3 mg of iodine did not persist for a long enough time for the effect to equal that of administering 6 mg daily. In other words, supplying 42 mg of iodine in fourteen days will rarely have as much effect as supplying 42 mg in seven days, the average rate that will produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston. It thus appears that iodine must be supplied to the thyroid gland at a certain minimum rate in order for the maximum effect to occur.

TABLE 5—*The Relation Between the Percentage Approach of the Basal Metabolism Toward the Normal Level and the Amount of Iodine Available for Storage of Colloid**

Daily Dose of Iodine, Mg	Number of Cases	Average Theoretical Amount of Iodine Necessary for Maximum Storage of Colloid,† Mg	Approximate Amount of Iodine Administered in Average Time Required for Maximum Reduction in Basal Metabolic Rate, Mg	Percentage Which the Amount of Iodine Administered Forms of the Amount Necessary for Maximum Storage of Colloid	Percentage Approach of Basal Metabolic Rate Toward the Normal Level
6	8	42	42	100	65
3	12	29	21	72	28
1.5	11	21	7.5	34	21
0.75	8	18	4.5	25	11

* This table applies only to cases in which the thyroid glands were weighed. Thus the figures in the last column are slightly different from those in the corresponding column of table 3.

† The iodine content of the thyroid after medication minus the iodine content before medication was started. In obtaining these figures, the amounts estimated from the figures of Marine and Lenhart, the Mayo Clinic and Cattell in table 4 were averaged.

PATIENTS SHOWING A RISE IN BASAL METABOLISM DURING THE ADMINISTRATION OF SMALL DOSES OF IODINE, FOLLOWED BY A DROP DURING THE IMMEDIATE SUBSEQUENT ADMINISTRATION OF LARGE DOSES

There were five cases that showed an increase in basal metabolism during the administration of from 0.75 to 3 mg of iodine daily, followed by a decrease during the immediate subsequent administration of much larger doses (table 6). In view of the level to which the basal metabolism fell during rest, the drop on all doses in these five cases was only 16 points (from plus 44 to plus 28 per cent), i. e., only about half as much as would be expected from initially giving large doses. Considering only the drop that occurred during the administration of large doses, it was fairly well marked (from plus 60 to plus 28 per cent), although the approach toward normal was less than that noted in initially giving 6 mg daily to the first series of hospital patients. In these cases, therefore, the small dose did in some way prevent the patient from receiving the maximum benefit from iodine. Since this occurred in 10 per cent of the cases in the 3 mg², 1.5 mg³ and 0.75 mg

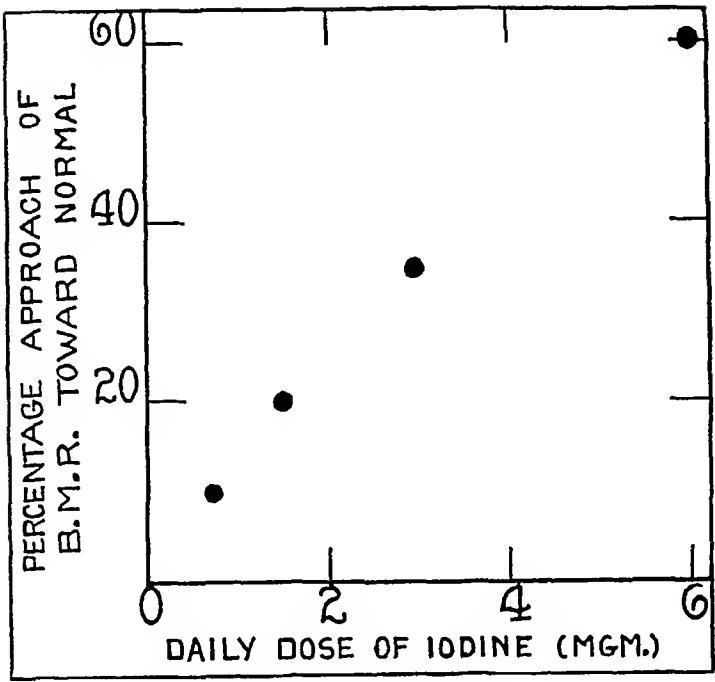


Fig 9—The relation between the dose of iodine and the percentage approach of the basal metabolism toward the normal level

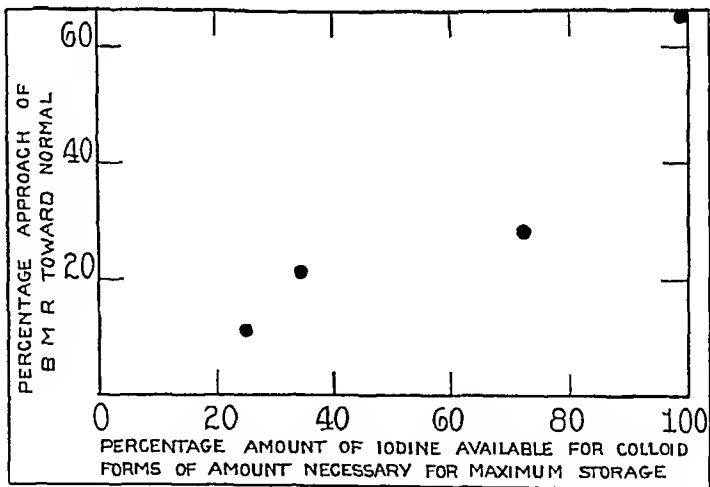


Fig 10—The relation between the percentage approach of the basal metabolism toward the normal level and the amount of iodine available for storage of colloid (see table 5)

series, since the rise on small doses was preceded by a drop with rest and was followed by a drop during the administration of large doses given immediately afterward, and since all these changes occurred in so short a time, it can scarcely be regarded as a coincidence that the basal metabolism rose during the administration of small doses. The data in this paper thus serve to support a conclusion previously reached, viz, that in a certain proportion of cases the reaction to iodine is a reversible one. In such cases it appears that if the amount of iodine administered is inadequate to imitate the change in the thyroid gland that is associated with a reduction in basal metabolism, it is utilized to

TABLE 6—*Patients Showing a Rise in Basal Metabolism During the Administration of Small Doses of Iodine, Followed by a Drop During the Immediate Subsequent Administration of Large Doses*

Patient	Laboratory Number	Basal Metabolic Rate on Admission	Level of Basal Metabolic Rate During Rest	Level to Which Basal Metabolic Rate Rose During Administration of Small Doses of Iodine	Level to Which Basal Metabolic Rate Dropped During Administration of Large Doses of Iodine	Approximate Size of Small Dose of Iodine, Mg Daily
Mrs G H	1340	+69	+48	+60	+33	0.75
Mr G C	6711	+38	+40	+48	+15	0.75
Mrs M S	6586	+98	+60	+68	+44	1.50
Mr T B	6185	+32	+23	+52	+27	3.00
Mr J B	6264	+48	+47	+70	+23	3.00
Average		+57	+44	+60	+28	

increase the output of the thyroid secretion, whereas if it is adequate to imitate this change, the output is diminished.

We wish to emphasize once again that the conclusions here reached can at present be said to apply only to the place from which the patients came, viz, Boston and vicinity.

SUMMARY

During the daily administration of about 0.75 mg of iodine in the form of the compound solution to twelve unselected hospital patients with exophthalmic goiter, four showed a reduction in basal metabolism of from 11 to 19 points, six showed no change and two showed an increase.

Whereas only 33 per cent of the patients showed a reduction in basal metabolism of 10 points or more during the daily administration of 0.75 mg, 50 per cent showed a reduction during the daily administration of 1.5 mg, 65 per cent during the daily administration of 3 mg, and 88 per cent during the daily administration of 6 mg.

The administration of about 0.75 mg a day caused an average reduction in basal metabolism of 4 points (from plus 39 to plus 35 per cent) as compared with 9 points (from plus 43 to plus 34 per cent) for 1.5 mg, 14 points (from plus 40 to plus 26 per cent) for 3 mg, and 27 points (from plus 36 to plus 19 per cent) for 6 mg.

Whereas the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most hospital patients with exophthalmic goiter in Boston is about 6 mg per day, the smallest amount that will produce any effect is greater than 0.75 mg per day in about two thirds of the cases, and is probably not much less than 0.75 mg per day in the other third.

Within these limits of dosage there appears to be roughly a linear relationship between the percentage approach of the basal metabolism toward the normal level and the dose of iodine.

It also appears that within these limits of dosage the reduction in basal metabolism is roughly proportional to the amount of iodine available for the storage of colloid.

In five of forty-six patients who received from 0.75 to 3 mg of iodine daily, the reaction to iodine appeared to be reversible, i. e., the basal metabolism rose during the administration of the small dose and fell during the immediate subsequent administration of a much larger dose.

Iodine must be supplied to the thyroid gland at a certain minimum rate in order for the maximum effect to occur.

CINCHOPHEN POISONING

AN ATTEMPT TO PRODUCE TOXIC CIRRHOSIS OF THE LIVER IN RATS *

HERBERT S REICHLE, M D

CLEVELAND

In a previous paper ¹ two cases of toxic cirrhosis were described that were observed clinically and examined at autopsy in the Cleveland City Hospital. Reports of many cases have since then appeared in the literature, cinchophen and its allies may now be regarded as drugs of considerable potential toxicity. Nevertheless, it remains true that cinchophen is used extensively without any apparent ill effects. It is, therefore, of considerable importance that the mechanism of the drug's toxic action be explained.

EXPERIMENTS

Adult albino rats were used in these experiments. They were fed dried whole milk, whole wheat flour, calcium carbonate, sodium chloride (Sherman's diet B) and weekly additions of meat and greens. In many of the rats infections of the upper and lower respiratory tracts developed, such as purulent bronchitis, pneumonia with atelectasis and disease of the middle ear, which were found with equal frequency among the controls.

The lethal dose of a single parenteral administration of cinchophen was first determined. Four rats weighing about 300 Gm. were given subcutaneously from 1 to 2 Gm. per kilogram of body weight of a suspension of the drug in acacia. All the animals died within twenty-four hours and exhibited profound disturbances of the central nervous system, such as listlessness, interference with the preservation of equilibrium and generalized convulsions, a tremendous diuresis and severe dyspnea. Microscopic examination of the organs, however, did not permit these symptoms to be ascribed to any specific toxic effect. The slides showed uniformly a poor staining quality of the tissue and extreme degeneration of the parenchyma of the liver, kidney and spleen. The necrotic cells exhibited a peculiar circumnuclear edema. The lymphatic tissue everywhere appeared to be depleted of cells.

* Submitted for publication, June 22, 1931.

From the Institute of Pathology and the Department of Pediatrics, Western Reserve University.

¹ Reichle, H. S. Toxic Cirrhosis of Liver Due to Cinchophen, Arch. Int. Med. 44:281 (Aug.) 1929.

These results are ascribed to a very gross form of poisoning, probably due to the acidity of the drug

In the second experiment, the dosage of the drug was reduced and only from 0.2 to 0.5 Gm per kilogram of weight was administered in the same manner. The injections were repeated daily for eight days. Dyspnea and diuresis were again observed. The animals lost weight, their fur was ruffled and disorganized, and the penis projected from the prepuce. However, there were no specific changes, the parenchymatous organs were in a state of severe cloudy swelling but the nuclei were well preserved. The liver, it is true, showed many focal necroses, circular areas that stained a uniform pink and that contained densely staining nuclei, apparently belonging to cells of the reticulo-endothelial system. Little importance is attached to these changes, since they are found in many toxic conditions in the rat, and particularly because rat 7, which was killed seventeen days after the last injection, had a normal histologic structure of the liver. In no case was there any evidence of connective tissue proliferation. Evidently, therefore, the changes observed in the rats killed during the course of the injections had been repaired by a *restitutio ad integrum*. The striking feature of the toxic cirrhosis caused by cinchophen is the incapacity of the organ to restore its parenchyma. There is destruction of parenchyma, proliferation of connective tissue and disorganization of the natural architecture. The severe nature of the hepatic injury has recently been well described by Beaver and Robertson.²

A subsequent attempt to develop specific damage by the use of the lowest dose (0.2 Gm per kilogram) over a longer period of time (thirteen injections) also failed. Again dyspnea was observed, there were periods of excitement and even collapse occurred immediately after an injection. After the last dose the experimental rats showed great uneasiness, the respirations were deep and panting, the gait was a wobble, and the head and anterior extremities were dragged along the floor. The animals sought the corners of their cages. Microscopic examination, however, again revealed nothing but the changes already described.

The parenteral administration of the drug having failed, the enteral route was next tried on the chance that the drug might by this path exert its full toxic action directly and immediately on the liver. Following a suggestion of Dr. Paul Klemperer of Mount Sinai Hospital, New York, this organ was first deprived of its store of glycogen, since

² Beaver, D. C., and Robertson, H. E. The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning, *Proc. Staff Meet., Mayo Clin.* 6: 216, 1931.

many researches (Fischler³) have shown the importance of carbohydrate in the protection of the liver against toxic agents of many different types. The rats were starved for five days. A control rat killed at this time demonstrated that all glycogen that can be obtained by hot alkaline extraction from the fresh liver had been removed. The animals, whose weights varied from 165 to 210 Gm., were given 20 mg. of cinchophen by mouth three times on the first day, and thereafter 4 mg. twice a day for ten days. A second period of starvation of twenty-four hours was followed by two days on which 60 mg. was administered each day, and from then on 10 mg. was given twice daily. The drug was administered suspended in olive oil. The animals were killed at the close of the experiment, after having taken 1,380 mg. each in seventy-two days. The results of histologic examination were entirely negative. In one rat uremia developed on the thirty-third day (after the administration of 576 mg. of cinchophen). Autopsy revealed an extraordinary degeneration of the cortical portion of the kidneys, the glomeruli had largely disappeared and were replaced by fibrous masses, which were in part calcified. The liver showed no changes that could not be considered a part of the uremic toxicosis. This was the only case of severe chronic organic disease not due to infection that was encountered. According to Jaffe,⁴ such renal degenerative disease occurs in the rat under laboratory conditions and is of unknown etiology. A second experiment of the same type as the preceding one, in which four rats were given 880 mg. of cinchophen per os in thirty-one doses, and three rats the same amount of neo-cinchophen, resulted in nothing more than a severe cloudy swelling of the liver. Neocinchophen was added in this experiment to determine whether this ester of cinchophen, which is regarded as entirely innocuous, might not possess the same toxic properties as cinchophen.

Further experiments followed the principle of a double hepatic injury. The liver of the experimental rat was injured with chloroform, and cinchophen was then administered per os. In one experiment the chloroform was given by inhalation to complete narcosis on four successive days. Seven rats were then given 20 mg. of cinchophen three times a day for twelve days. At autopsy no gross changes were seen. Unfortunately, the specimens were lost, so no microscopic

3 Fischler, F. Ueber Probleme des Kohlenhydratstoffwechsels mit besonderer Berücksichtigung der Rolle der Leber, *Deutsche med. Wchnschr.* **55** 605, 1929, Zur Chemie und zur therapeutischen Wirkung des Traubenzuckers, *München med. Wchnschr.* **75** 1541, 1928, Traubenzucker als Therapeutikum, *ibid.* **76** 791, 1929.

4 Jaffe, R. Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere, Berlin, Julius Springer, 1931.

report can be given. In the second experiment of this type, the chloroform was given subcutaneously in solution with olive oil. It was found that this method was the least dangerous and the most accurate in dosage. The animals appeared to suffer no pain and were quite drowsy. A total of from 0.33 to 0.75 Gm of chloroform was given in three days. Postmortem examination of one animal which had received 0.57 Gm in four days showed the presence of a large fatty, hemorrhagic, friable liver. The remaining rats were then given 300 mg of cinchophen in ten days and were killed five days after the last dose. Histologic examination revealed no pathologic changes of importance. These experiments show that, at least in the rat, it is not possible, by the ordinary methods, to reproduce the toxic cirrhosis characteristic of cinchophen poisoning.

In a previous article¹ I stated "that there is little doubt but that natural idiosyncrasy may be of importance. It is also thought that idiosyncrasy may be artificially induced. Worster-Drought's⁵ patient, after having taken 370 grains in twelve days developed urticaria, which disappeared when the medication was stopped. One dose of 7.5 grains administered three weeks subsequently brought on urticaria, gastro-intestinal disturbance and jaundice, which lasted ten days." Evans,⁶ Anderson and Teter⁷ and Barron⁸ reported the same experience. Barron's case showed a particularly exquisite manifestation of hypersensitiveness which occurred in a patient who had had previous medication with cinchophen. Immediately following the renewal of the drug a severe reaction occurred, which repeated itself on a third attempt to use cinchophen. Barron called attention to the patient described by Boots and Miller who reacted adversely to the first administration of cinchophen. Schwann⁹ used atophanyl, a cinchophen preparation for intravenous use. He observed severe prostration after the first injection in one patient. There were anginal pains, vasomotor disturbances, unconsciousness, cyanosis and profuse sweating. In another case the untoward reaction was seen after the third injection. The patient became restless, and a chill, angioneurotic edema of the face and severe urticaria developed. It is true that not all cases show these classic symptoms, nor is the course always char-

5 Worster-Drought, C. Atophan Poisoning, *Brit M J* **1** 148 (Jan 27) 1923

6 Evans, Geoffrey. Discussion, *Brit M J* **2** 689 (Oct 16) 1926

7 Anderson, S. D., and Teter, D. P. Acute Yellow Atrophy of the Liver Following Administration of Oval Iodide, *J A M A* **93** 93 (July 13) 1929

8 Barron, M. Cinchophen Poisoning, *J A M A* **82** 2010 (June 21) 1924

9 Schwann, W. Unerwünschte Atophanwirkung, *Klin Wchnschr* **3** 935, 1924

acteristic. There are probably several different reasons for this. The drug is often continued long after the toxic symptoms have manifested themselves (as in my own cases¹ 1 and 2). Again, not always do all of the most striking symptoms of hypersensitiveness appear. There are, moreover, two types of sensitivity. In the one, the patient is primarily sensitive (Boots and Miller's case, cited by Barron⁸), in the other, the sensitivity is probably acquired (Worster-Drought⁵). It is particularly the latter type that is most interesting, since it shows a close relationship of this sensitivity to others which, because of the therapeutic importance of the drugs involved, have been more closely studied. The reactions to arsphenamine and sensitivity to nirvanol (phenyl-ethyl-hydantoin) are examples.

Nirvanol, which was originally used as a sedative and hypnotic, was abandoned because of the rashes that frequently followed its use. The German pediatricians observed a uniformity in the course of the rash due to nirvanol, or, more properly, the sickness due to this medication. In a large percentage of the patients who were treated with this drug a severe morbilliform eruption occurred from the seventh to fourteenth day of administration. Following this reaction, the patients (the condition was chorea) showed remarkable improvement. Since then these observations have been verified by many investigators. A discussion of the results is given in the paper by Pilcher and Gerstenberger¹⁰. It is important to note that the rash is only the external, and not a necessary, manifestation of a general reaction of the body to the drug. This is characterized by fever and changes in the metabolism, which are independent of the pyrexia (Beck¹¹), relative and absolute lymphocytosis and eosinophilia.

It appears that the reaction to cinchophen is probably of the same type. The symptoms are strikingly allergic: a rash, often urticarial, edema, vasomotor changes, sweating, disturbance of the oxygen exchange and vomiting. The free interval, the frequency of "safe" previous medication, the appearance of the symptoms after the drug has been stopped, which reminds one of serum sickness, the lack of premonitory symptoms and the acuteness of the onset are suggestive of a hypersensitive state. The toxicity does not depend on dosage. Some of the patients received small amounts, others large doses over long periods of time. In all cases the onset is relatively acute. It is beyond the scope of this report to enter into a discussion of the nature of this sensitivity. In my opinion, the reactions fall into the realm

10 Pilcher, J. D., and Gerstenberger, H. J. Treatment of Chorea with Phenyl-Ethyl-Hydantoin, *Am J Dis Child* **40** 1239 (Dec.) 1930.

11 Beck, O. Ueber Veränderungen des kindlichen Stoffwechsels bei Nirvanol-Zufuhr. *Monatschr f Kinderh* **45** 486, 1930.

of the anaphylactoid (Hanzlik and Karsner¹²) Karsner¹ enumerated the following symptoms "increased reflex excitability, rapid respiration and dyspnea, sneezing, retching, jerky spasms, slowing or acceleration of the heart trembling, expulsion of urine, cyanosis, pupillary relaxation, convulsions and death with large doses—all of which have also been described in cases of cinchophen poisoning. Some of these symptoms were observed by me in the course of the parenteral administration of the drug to rats. With animals more susceptible to allergic manifestations it might have been possible to obtain more convincing evidence. It is also possible that cinchophen poisoning is precipitated by a reaction of various antibodies with this nonantigenic compound, as Landsteiner¹⁴ has proved for metanilic acid, para-arsenic acid and *p*-amino benzoic acid. Following this thought, we may perhaps conceive of a similar mechanism by which the drug combines with a protein of the subject to form a complex compound of protein and nonprotein radicals. As Landsteiner has shown, the non-protein radicals can react with the immune serum of animals treated with the entire compound and of themselves saturate the specific antibody. Perhaps in vivo they might cause such hypersensitive conditions as are observed in phenyl-ethyl-hydantoin and cinchophen poisonings.

CONCLUSIONS

Subcutaneous administration of cinchophen in single doses of 1 Gm per kilogram of body weight killed rats within twenty-four hours. Continued parenteral administration of smaller doses (0.2 Gm per kilogram) did not cause death but after the last two injections, the rats displayed symptoms that may possibly be regarded as expressions of hypersensitiveness. Feeding of cinchophen in doses of approximately 20 mg a day to rats when the livers had been depleted of glycogen by starvation or injured by chloroform did not induce cirrhosis. No characteristic changes in the histologic appearance of the organs were found on postmortem examination.

A review of the histories of cases of reaction to cinchophen suggests that its cause may be found either in a natural hypersensitiveness or in the development of a hypersensitive state.

12 Hanzlik, P. J., and Karsner, H. T. Anaphylactoid Phenomena from Intravenous Administration of Various Colloids, Arsenicals and Other Agents, *J. Pharmacol. & Exper. Therap.* **14** 379 (Jan.) 1920, Effect of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Bronchi of Perfused Lungs, *ibid.* **14** 449 (Feb.) 1920.

13 Karsner, H. T. Anaphylaxis and Anaphylactoid Reactions, in Jordan, E. O., and Falk, I. S. *The Newer Knowledge of Bacteriology and Immunology* Chicago University of Chicago Press, 1928 p. 985.

14 Landsteiner, K. *Biochem. Ztschr.* **93** 106, 1919 **104** 280, 1920.

BLOOD SUGAR IN MAN FOLLOWING THE RECTAL ADMINISTRATION OF DEXTROSE*

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AND
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The dextrose retention enema is such a common clinical procedure, and the impression that considerable amounts of dextrose are absorbed after rectal administration is so well established in spite of the conflicting nature of the experimental data submitted in evidence that we considered the problem worthy of further investigation.

Clendenning¹ recommended such enemas, quoting Edsall to the effect that nine tenths of the carbohydrate injected is "taken up by the rectum." Sollmann² stated that dextrose is "absorbed effectively from nutrient enemas." Lutje treated diabetic acidosis by rectal injections of sugar, and Joslin³ noted that as long ago as 1904, Ainhem reported that acetonuria of diabetic patients was diminished after the rectal administration of sugar solutions. Tallerman⁴ reported an elevation of the blood sugar curve in some of his cases. Carpenter⁵ stated that the absorption may be as much as 90 per cent of the dextrose administered. Varela and Rubino⁶ reported glycosuria in seven of seventeen cases following the administration of a sugar solution by means of a rectal drip. Hari and von Halasz⁷ approached the problem through a study of the respiratory gases and reported a rise of the respiratory quotient after rectal administration of dextrose. Carpenter⁵ reported similar results, but both he and Piessman⁸ warned against accepting a rise in the respiratory quotient as necessarily indicating that a considerable amount of sugar has been absorbed.

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* From the Department of Physiology, Columbia University

1 Clendenning, L. Modern Methods of Treatment, ed 2, St. Louis, C. V. Mosby Company, 1928

2 Sollmann, T. A Manual of Pharmacology, ed 3, Philadelphia, W. B. Saunders Company, 1926

3 Joslin, E. P. The Treatment of Diabetes Mellitus, ed 4, Philadelphia, Lea and Febiger, 1928

4 Tallerman, K. H. Quart. J. Med. **13** 356, 1920

5 Carpenter, T. M. Human Metabolism with Enemata of Alcohol, Dextrose and Levulose, Publ. Carnegie Inst., Washington, D. C., Dec., 1925

6 Varela and Rubino. Med. Klin. **26** 831, 1922

7 Hari, P., and von Halasz, A. Biochem. Ztschr. **88** 337, 1918

8 Pressman, J. Am. J. M. Sc. **179** 520, 1930

Levi⁹ seems to believe that the rectal administration of dextrose is of little practical value. Mekie and Miller¹⁰ found no consistent change in blood sugar value. Franke and Wagner¹¹ reported varying results with three dogs. Pressman, and Rubino and Varela¹² reported a drop in the blood sugar curve.

The amount of dextrose returned in the stools after the enemas have been retained for some time has been investigated by many observers. Pressman⁸ reported about 25 per cent recovered after four hours. McNealy and Willems¹³ were able to recover about 98 per cent from the colon of dogs after one hour. Varela and Rubino⁶ recovered about 60 per cent. Various percentages are reported by other authors, and while there appears to be no agreement as to the actual amount that may be recovered after a definite period, all who have investigated this aspect of the problem have reported substantial returns.

That the bacterial flora of the large bowel plays no inconsiderable part in the problem has been shown by Bingel (quoted by Pressman⁸), who was able to cause the disappearance of about 30 per cent of the sugar by incubating it with feces for five hours. Pressman⁸ himself reported the loss of 90 per cent after seven hours' incubation.

The great diversity of results that appear is undoubtedly bound up with the widely differing material and methods that have been used in attacking the problem. The subjects have been sick men, well men, anesthetized men, men who had just recovered from an operation and anesthetized dogs. The sugar solutions have been administered as drip or retention enemas, and in the latter event the volume injected has varied from 180 to 600 cc., while the concentration has been almost anything from an isotonic to a 50 per cent solution. In few instances is any specific mention made of the brand of dextrose used. The methods employed for the determination of the blood sugar have varied widely. Finally, in spite of the rather voluminous literature on the subjects, there has been only a comparatively small number of actual cases reported.

In the belief that a significant norm would be of value not only in forming an opinion but as an aid to future work, we have approached the problem from a statistical standpoint. We felt that there was nothing in the previous work to prove that a small constant deviation in the blood sugar curve might not have been overlooked. Our approach has been physiologic rather than clinical. We wish to emphasize that

9 Levi, D. *Brit J Surg* **15** 282, 1927.

10 Mekie, E., and Miller, H. *Brit M J* **1** 244 (Feb 9) 1929.

11 Franke, W., and Wagner, R. *J J Metab Research* **6** 375, 1924.

12 Rubino and Varela. *Klin Wchnschr* **1** 2370, 1922.

13 McNealy, R. W., and Willems, J. D. *Surg Gynec & Obst* **49** 794, 1929.

we are concerned primarily with the blood sugar curve as such, and to point out that variations in that curve, or the lack of them, or variations in the respiratory quotient, cannot be definitely correlated with the absorption of specific amounts of sugar

According to one of us (Dr Scott¹⁴) our first few results showed such a deviation as to indicate that at least fifty cases would have to be studied before a definite conclusion would be warranted

EXPERIMENTAL DATA

Our subjects were healthy, first year medical students. They reported to the laboratory after a twelve hour fast and were given a preliminary enema of 200 cc of warm tap water. This was passed at once, and the blood sugar concentration during fasting was determined. The subjects were then given solutions of dextrose of varying concentrations by rectum, which they retained for two or three hours. At the end of this time the enemas were returned, and their sugar

TABLE 1—*Blood Sugar per Hundred Cubic Centimeters at Varying Periods After the Administration of 200 Cc of 10 Per Cent Dextrose Solution by Rectum*

Body Weight, Pounds	Fasting	½ Hr	1 Hr	1½ Hr	2 Hr	2½ Hr	3 Hr	Stool Return, Gm
155	114	102	113		121		100	
170	118	117	110	107	122	117	122	17
	106	103		108	113		114	
150	104	105	99		106	111		23
115	118	101	90	94	112	100		60
145	114	99	94	97	97	97		
184	114	111	107	106	107	110		20
140	103	95	91	96	99	98		52
185	111	105	105	103	98	103		53
Averages	111	104	101	102	108	105	112	

content was found by a modification of the Benedict quantitative method for determining urinary sugar. About one half of the subjects were given additional enemas of tap water at the close of the experiment to wash out the rectum, but these showed no significant increase in the amount of dextrose returned over that obtained from those in whom this process was omitted. During the time the enema was retained, samples of blood were drawn from veins in the arm at specified intervals and their sugar content determined by the method of Shaffer and Hartmann¹⁵. The sugar values were calculated from the table¹⁶ of Duggan and one of us (Dr Scott). The determinations were made in duplicate, the values reported being the averages of the duplicate determinations. The blank spaces on the charts represent points at which, for various reasons, such as marked disagreement between two tubes or difficulties in the class schedules of the student subjects, the figures could not be obtained. About 10 per cent of the subjects reclined on a bed during the entire period of the experiment, the remainder went about the building to their classes, returning at stated intervals for the withdrawal of samples of blood.

14 Scott, E. L. *J. Biol. Chem.* **73** 81, 1927

15 Shaffer, P. A., and Hartmann, A. F. *J. Biol. Chem.* **45** 365 (Jan.) 1921

16 Duggan, W. F., and Scott, E. L. *J. Biol. Chem.* **67** 287, 1926

We attempted to use moderately high concentrations in a few cases. These solutions caused so much discomfort, such as pain, urgent desire to defecate and nausea, that we were forced to abandon them in favor of more dilute solutions. Four hundred cubic centimeters of a 10 per cent solution could be retained without much annoyance.

To each of a group of four subjects, 200 cc of 10 per cent dextrose solution was given by mouth. The blood sugar curve for this group showed the usual

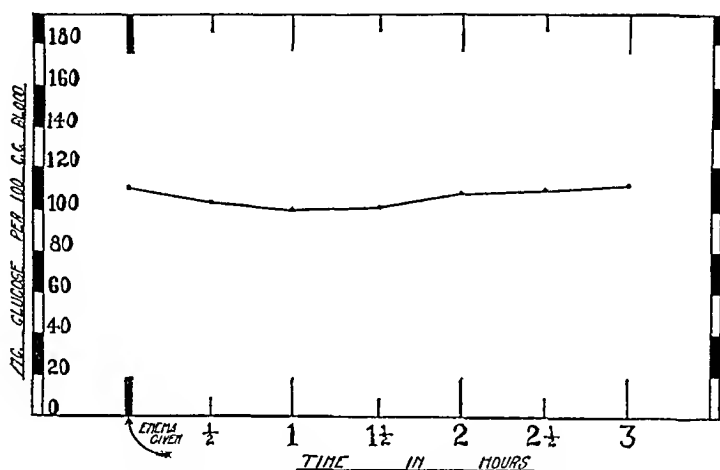


Chart 1—Graph of the results of the administration of 200 cc of 10 per cent dextrose per rectum

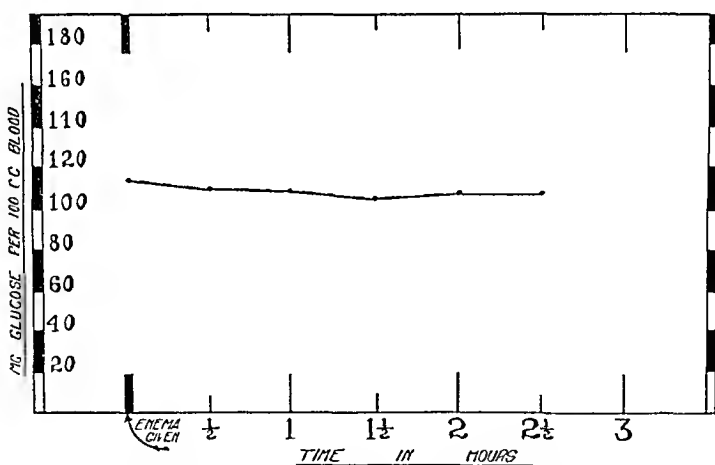


Chart 2—Graph of the results of the administration of 400 cc of 10 per cent dextrose per rectum

alimentary rise at the end of thirty minutes and one hour. Three subjects were given 180 cc of 15 per cent solution by rectum, and no significant deviation from the fasting level was noted in their blood sugar curves over a period of two and one-half hours. Three subjects, who were given 180 cc of 30 per cent dextrose solution, were unable to retain the enema longer than half an hour. At that time, their blood showed no significant change in its sugar level. Nine subjects were given 200 cc of a 10 per cent dextrose solution by rectum. The arithmetical means for this group show a drop of 10 mg per cent at one hour (table 1, chart 1). In

view of the small number in this series and the relatively large deviations, we do not consider that at present a definite significance can be attached to this drop

Fifty subjects were given 400 cc of a 10 per cent solution of dextrose by rectum (table 2, chart 2) The arithmetical mean for this group shows a gradual

TABLE 2—*Blood Sugar After the Administration of 400 Cc of 10 per Cent Dextrose Solution by Rectum*

Body Weight, Pounds	Fasting	½ Hr	1 Hr	1½ Hr	2 Hr	2½ Hr	Stool Return, Gm
175	103	102	96	93	97	94	11 1
160	107	91	97	96	94	108	5 0
140	92	103	99	98	105	102	9 9
156	110	103	110	97	97	99	8 6
124	97	87	99	94	94	93	10 1
180	118	113	118		115		19 0
		122	116		121		21 0
145	125	116					3 5
125	107	99	93		103		21 0
	117	119	120		119		18 0
			105		105		8 6
148	107	110	105		103		15 0
	125	137	123		116		10 0
160	110	114	101		109		18 0
155	125	118	125		118		21 0
170	86	87	84		84		17 0
165	124	110	105		105		19 0
155	101	105	104		99		8 0
170	110	107	108		108		13 0
140	102	97	102	92	99	103	32 0
160	101		107	108	108	110	3 0
165	100	108	96	105	93	104	15 0
180	123	113	123	117	113	112	18 0
125	119	123	119	114	113	115	
180	118	117	108	109	102	103	17 0
145	110	102	103	102	113	102	9 0
180	130	117	118	118	116	111	1 0
134	135	128	118	113	116	121	13 0
196	120	115	115	116	114	119	15 0
113	155	120	96	106	105	135	0 6
135	106	106	103	108	112	109	22 0
160	124	118	112	121	121	120	2 0
180	111	75	119	115		110	19 0
155	128	131	125	121	120	125	11 0
138	105	109	113	108	108	104	4 7
140	118	115	112	107	107	114	1 8
135	107	97	109	99	107	105	2 0
139		108	106	101	101	100	0 8
155	103	99	108	97		98	5 7
162	107	112	102	105		98	14 0
165	117	110		114	112		
138	103	105	102	100	100	100	8 0
200	106	99	102	104	108	107	10 2
145	104	107	102	102	102	97	7 1
155	119	118	124	109	124	124	15 8
180	106		98	99	109	104	15 8
160	119	109	110	105	112	104	18 0
147	110	112	107	96	105	103	19 5
147	107	99	103	105	99	101	5 3
135	125	110	102	103	104	113	9 8
Number of de terminations	48	47	48	36	46	35	48
Average	113 0	108 9	107 8	105 5	107 3	107 4	
ϵ^*	13 8	11 5	9 4	8 0	8 6	9 2	
ϵ_{N}^*	1 7	1 7	1 3	1 3	1 3	1 8	

* Scott (footnote 14)

fall in the blood sugar curve, the lowest point is reached one and one-half hours after the administration of the dextrose This point is 75 mg per hundred cubic centimeters below the fasting level The values for ϵ^{14} are, however, of such an order that we cannot say that the drop is definitely significant

The figures for the dextrose in the returned enemas are highly variable, it is worthy of note, however, that in thirty-one of fifty-four cases, one quarter or more of the administered dextrose was returned, and in five instances, over one-half was returned.

The sugar that was not recovered in the stools may possibly have risen higher in the large bowel because of antiperistalsis or for some other reason, there to be retained for a slow absorption, partial destruction by fermentation or a later return. A certain amount may have entered the blood stream at a rate too slow to elevate the blood sugar concentration significantly. The drop in the curve, if in fact there is an actual drop, might be taken to indicate that there has been absorption of an amount sufficient to stimulate the outpouring of insulin.

CONCLUSIONS

1 It has not been possible to demonstrate a rise in the blood sugar curve as a result of administering dextrose in retention enemas.

2 The slight drop that our curves show may be due to a stimulation of pancreatic activity brought about by the absorption of a slight amount of dextrose, or, more probably, to chance variation.

3 A variable and frequently considerable amount of dextrose administered by enema may be recovered from the stools after two and one-half hours.

VISCEROCARDIAC REFLEXES

AN EXPERIMENTAL STUDY IN FROGS AND DOGS

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AND

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The impression that visceral excitation may produce reflex alteration of cardiac activity is rapidly gaining ground in the clinical literature. Occasionally, even the death of the patient has been attributed to such a reflex disturbance. Of all the viscera that may influence the heart reflexly, the gallbladder and the biliary passages have been most suspected. Osler¹ and Albutt² cited instances in which patients died during gallstone colic and ascribed the death to reflex vagal inhibition. Others³ have commented on the relation of cardiac arrhythmia to gallstone colic. Several writers⁴ have reported a series of cases showing that myocarditis and cholecystitis are so frequently associated that some meaning for the association probably exists. Babcock,⁵ Mayo,⁶ Strauss and Hamburger⁷ have reported cases of cardiac disorders in which improvement occurred after operation was performed on the biliary tract.

That cardiac irregularities may be induced reflexly from visceral excitation is supported by certain experimental evidence. The well known Goltz experiment, in which tapping of the viscera in the frog

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* From the Department of Physiology and Pharmacology, Northwestern University Medical School

1 Osler, William, cited by Babcock, R H. *Ann Clin Med* **2** 203, 1922

2 Albutt, C, cited by Babcock (reference 1)

3 Reisman, D. The Development of Cardiac Murmurs During Attacks of Biliary Colic, *J A M A* **48** 1589 (May 11) 1907. Kulbs. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1914, vol 2, p 1239. Umber. *ibid* vol 3, pt 1, p 115. Lichty, M J. *Ohio State M J* **11** 779, 1915

4 Schwartz, M, and Herman, A. *Ann Clin Med* **4** 783, 1931. Willius, F A, and Fitzpatrick, J M. *J Iowa M Soc* **15** 589, 1925. Leech, C B. *New England M J* **26** 1318, 1929

5 Babcock (reference 1). The Diagnosis of Chronic Cholecystitis Complicating Cardiac Lesions, *J A M A* **73** 1929 (Dec 27) 1919

6 Mayo, W J. *Illinois M J* **45** 33, 1924

7 Strauss, D G, and Hamburger, W W. The Significance of Cardiac Irregularities, *J A M A* **82** 706 (March 1) 1924

causes reflex slowing of the heart, is the oldest evidence bearing on this question. More recently Carlson and Luckhardt⁸ stated as a result of their experiments that "in the frog stimulation of the lungs the gastro-intestinal tract and genito-urinary tract causes reflex cardiac inhibition. In curarized preparations the reflex fails owing to vagus paralysis." This is approximately true for the salamander. But in the turtle stimulation of the large and small intestine, the urinary bladder and the cloaca in noncurarized animals causes chiefly an acceleration of the heart rate with a rise in blood pressure. In discussing the symptoms produced by distention of the gallbladder and biliary ducts in dogs, Schrager and Ivy⁹ reported that changes in blood pressure and heart rate are caused, which, however, are not uniform. They expressed the belief that the reaction of the cardiovascular system to distention of the biliary passages is dependent on the functional state of the cardiovascular system at the time the distention occurs.

Buchbinder¹⁰ has reported some interesting experiments in the frog in regard to the effects of incision of the gallbladder on cardiac activity. He observed that simple incision of the gallbladder in the frog causes a transient arrest of the heart, lasting from one to ten seconds, followed by a sinus bradycardia lasting from one to ten minutes. Occasionally, he observed dilatation and permanent arrest. These effects were attributed to a reflex vagus inhibition due to the acute change in pressure in the biliary tract incident to the incision of the gallbladder.

Because of the important clinical aspect of this experimental work, we decided to repeat it and to attempt a further analysis of the experiments. For example, in Buchbinder's experiment, the spillage of bile into the peritoneal cavity might play a rôle in the causation of the phenomenon he observed. He thought of this possibility, but discredited it by the statement that frog's bile in the amounts present in the gallbladder is innocuous for the heart. Therefore, in our experiments we have given particular attention to the spillage of bile and intestinal contents.

EXPERIMENTAL RESULTS

Since our experiments were performed on 130 frogs and 10 dogs, it is impracticable to give the protocols or details of the experiments. We shall merely summarize the results of the different groups of experiments.

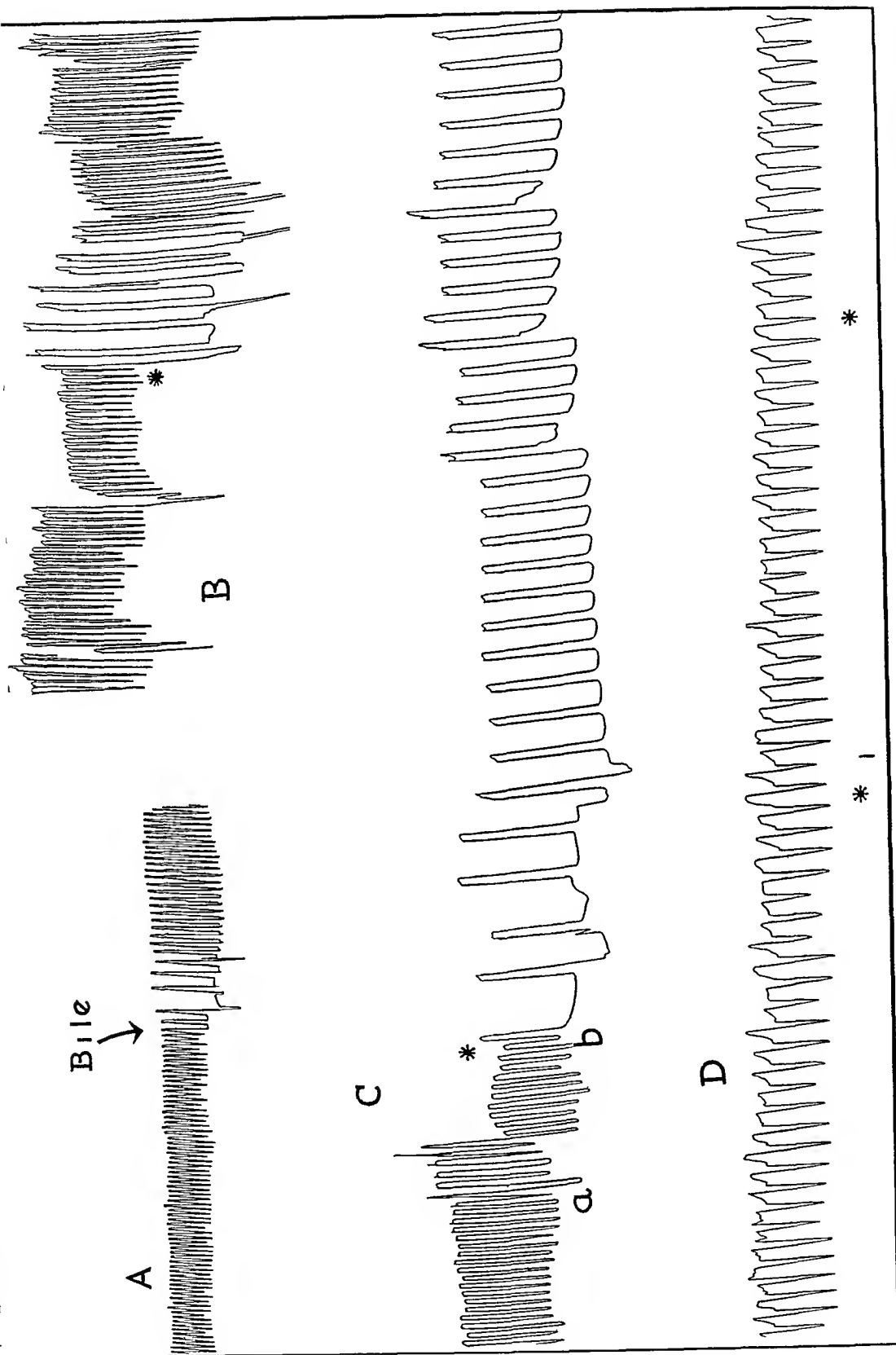
8 Carlson, A. J., and Luckhardt, A. B. *Am J Physiol* **55** 31, 1921.

9 Schrager, V. L., and Ivy, A. C. *Surg, Gynec & Obst* **47** 1928.

10 Buchbinder, W. C. *Proc Soc Exper Biol & Med* **27** 542, 1930, *Experimental Obstructive Jaundice*, *Arch Int Med* **42** 743 (Nov) 1928.

The results in the frogs were uniform under certain conditions. It was found that in order to obtain viscerocardiac reflexes in the frog, it must not be anesthetized and must be fully recovered from the shock incident to decerebration, the reflexes being obtained best in intact frogs, and then only in about one half of the frogs used. All frogs were anesthetized during the operative procedures of decerebration, spinal pithing, demedullation and exposure of viscera for stimulation, but in every instance sufficient time was allowed for the effect of shock and anesthesia to pass away. The observations of Carlson and Luckhardt⁸ on the cardio-inhibitory effect of traction, pinching the abdominal and pelvic viscera in the frog, were confirmed. No effect was observed unless the medullocardiac reflex mechanisms remained intact.

Ninety-nine of the experiments on frogs were directed to a study of stimulation of the gallbladder and spillage of bile. It was found that incision of the gallbladder in the decerebrate or intact frog caused cardiac inhibition uniformly and sometimes permanent (one-half hour) cardiac arrest, which confirmed the observations of Buchbinder. If pressure was exerted on the gallbladder or biliary tract area or if they were pinched, cardiac inhibition did not result. However, if this procedure was carried out so that traction was exerted on the liver or portal elements, cardiac inhibition would sometimes result. Also, if the bile was withdrawn by syringe and needle or prevented from spilling into or excluded from the peritoneal cavity, no cardiac inhibition would result. Further, if the cystic duct was carefully tied and the gallbladder with its bile carefully removed, inhibition would not occur. When the excised gallbladder containing bile was incised so that the bile spilled into the upper peritoneal cavity, cardiac inhibition occurred. Or, if bile was withdrawn from the gallbladder into a syringe and then slowly ejected from the syringe on to the abdominal viscera, the heart was inhibited. The inhibition of the heart following the contact of from 0.1 to 0.3 cc of bile with the peritoneum was not due to the fact that the bile spread upward and bathed the heart, since this can easily be prevented in most frogs. The direct application of frog's bile (from 0.1 to 0.3 cc) to the heart or to the pelvic peritoneum or the injection of bile into the dorsal lymph sac in the recovered decerebrate frog causes no alteration in the cardiac rhythm. It was noted that the intensity of the effect depended to a certain extent on the character of the bile. The darker, more concentrated bile had a more marked effect. There was also a quantitative relationship between the amount of bile released into the peritoneal cavity and the type and duration of the effect. It was noted that small quantities of less concentrated bile produced an initial acceleration of the heart rate and in two instances this was the only effect. A second application of bile to the same area of the



Tracing *A* shows the effect on the heart of a frog of 0.1 cc. of bile from another frog injected into the upper peritoneal cavity. Tracing *B* shows the effect on the heart of an incision of the gallbladder, without the bile coming into contact with the heart. Tracing *C* shows *a*, no appreciable effect on withdrawal with a syringe of the bile from the gallbladder, and *b*, the effect of introducing the withdrawn bile into the upper peritoneal cavity in the region of the gallbladder. Tracing *D* shows no effect produced by distention of the gallbladder and biliary passages.

peritoneal cavity of the recovered decerebrate frog caused no further change in the cardiac rhythm in the presence of the persisting bradycardia. In most instances the presence of an intact medullocardiac reflex mechanism was necessary for the effect, but inhibition occurred in three of fifteen experiments. The cardiac inhibition caused by spillage of bile into the peritoneal cavity is more marked and uniform than that caused by tapping, pinching or stretching the abdominal viscera, and makes a striking classroom demonstration. In view of these observations, we attribute the effects of incision of the gallbladder on the heart rate in the frog to spillage of bile into the peritoneal cavity. The presence of bile in the peritoneal cavity chemically instead of mechanically excites a reflex mechanism that results in cardiac inhibition, bradycardia or arrest.

In six frogs the gallbladder was cannulated, and the gallbladder and biliary passages were distended. In four no change in the heart was noted, in one the rate was slightly decreased, and in one the rate was definitely accelerated.

The effect of dog's gallbladder bile and hepatic bile in the upper peritoneal cavity of unanesthetized dogs on the cardiac rhythm and the blood pressure was studied in five animals. Blood pressure tracings were made on unanesthetized dogs with previously exteriorized carotid arteries simultaneously with the introduction of the bile (from 25 to 50 cc) by means of a hollow needle and syringe into the upper peritoneal cavity. A slight rise in blood pressure and an acceleration in cardiac and respiratory rates were the only effects noted in these experiments.

In five other dogs the effect of distention of the extrahepatic ducts was studied. The cystic duct was cannulated after ligation of the common duct, and the carotid artery on one side was exteriorized. The cannulated duct was connected to a rubber tube that was brought to the outside through the abdominal incision. The next day, blood pressure tracings were made of the unanesthetized dogs, and the effect of distending the ducts with air was noted. In one dog the initial distention of the ducts caused a marked slowing of the respiratory and cardiac rates. In the other dogs no definite uniform effect was obtained.

COMMENT

The results of the experiments on the frog show decisively that the chemical and mechanical stimulation of most abdominal viscera in the frog may reflexly excite the cardio-inhibitory mechanism. We were somewhat surprised and disappointed to find that mechanical stimulation and even distention of the frog's gallbladder and biliary passages had no effect on the cardiac rhythm analogous to that sometimes observed

when a similar stimulus was applied to the stomach or the intestines. It is worthy of note that traction on the liver or portal elements sometimes had an inhibitory effect, however, because of the close anatomic relationship of the liver to the heart this is difficult to interpret, although it was not observed to occur in demedullated frogs.

The interesting observation of Buchbinder¹⁰ on cardiac inhibition following incision of the gallbladder is due, as our results show, to local chemical irritation by the bile of nerve endings in the peritoneum or surrounding organs which reflexly excites the cardio-inhibitory mechanism. The failure to obtain cardiac inhibition in the dog when bile was injected into the peritoneal cavity (we observed acceleration) shows that the viscerocardiac reflex mechanisms are different from those of the frog. Carlson and Luckhardt⁸ found this to be the case in the turtle.

The results on distention of the biliary passages of the dog confirm but are not so striking as those of Schrager and Ivy,⁹ who observed extrasystoles in one dog. The effect on the heart and blood pressure is not uniform. Either inhibition or acceleration of the heart may result. The best explanation of this variation is that suggested by Schrager and Ivy, namely, 'that the reaction of the cardio-vascular system to distention of the biliary passages is dependent on the functional condition of the cardio-vascular system at the time the distention occurs.' The effect of distention of the biliary passages in the frog was even less effective than in the dog. In the cat a rise in blood pressure (pain?) occurs on distention of the common bile duct without a decided change in the heart rate.¹¹

The experimental evidence does not indicate positively the existence of a direct reflex connection between the biliary passages and the cardiac activity, since a definite disturbance of the heart on stimulation of the biliary tract is the exception rather than the rule. It must be kept in mind, however, that in the experiments performed on dogs and frogs up to the present time, only normal mechanisms have been excited presumably. Whereas the patients considered in this discussion have a pathologic condition of the biliary tract and, in some instances at least, an abnormal heart and possibly in all cases a functionally "abnormal" or "irritable" heart. Experiments are yet to be done on animals with an abnormal condition of the biliary tract and heart. Also, the cardiac disturbances associated with disease of the biliary tract or visceral disease in general may not be due primarily or directly to a viscerocardiac mechanism but secondarily to the cardiocirculatory changes known to be caused by nausea, vomiting, pain and respiratory disturbances. Of

11 Sherrington, C. S. *Integrative Action of the Nervous System*, New Haven, Yale University Press, 1920, p. 11.

course, man may possess a direct or more sensitive viscerocardiac mechanism, this is not likely, since all patients with pathologic conditions of the biliary tract or other viscera do not manifest cardiac abnormalities

CONCLUSIONS

The observations of Carlson and Luckhardt⁸ on the cardio-inhibitory effect of mechanical stimulation of the abdominal and pelvic viscera and on the reflex mechanism concerned in this effect have been confirmed.

The gallbladder and biliary passages may be pinched and stretched without causing a change in the cardiac rhythm of frogs that show cardiac inhibition on mechanical stimulation of other abdominal viscera. The distention of the biliary passages in the frog usually causes no change in the heart, although either slight slowing or acceleration in rate occasionally may be observed.

The incision of the gallbladder of the frog so that bile is spilled into the upper abdominal cavity without coming in contact with the heart causes cardiac inhibition, which is due to a reflex inhibition of the heart caused by the irritant action of bile on the peritoneum and not to the toxic action of bile on the heart. Bile introduced into the upper portion of the peritoneal cavity of the dog causes acceleration of the heart instead of inhibition.

The observations of Schragar and Ivy on the effect of distention of the biliary passages in the "normal" dog have been confirmed essentially, a slowing of cardiac rate being observed in one of five dogs and no definite or uniform effect being observed in the others.

The bearing of these results on the alleged association of disease of the biliary tract with cardiac abnormalities in man is briefly discussed.

EXPERIMENTAL STUDIES ON THE EFFECT OF SECTION OF THE VAGUS NERVE ON GASTRIC SECRETION *

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AND

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Much interest has been manifested in recent years concerning the effect of section of the vagus nerve on the functions of the stomach. This procedure has been performed experimentally in animals and is now frequently recommended in gastric surgery in the treatment for peptic ulcer. It is commonly reported that there is a decrease in the gastric acidity after section of this nerve following subtotal gastrectomy. Considerable literature on this subject has accumulated in recent years. It may be said in general that most observers have noted a decrease in the gastric secretion following vagus section. It, however, appears from the literature that in the larger proportion of these experiments the observations have been followed only for a short period of time. What the results might have been after prolonged observations of these animals has up to the present not been clearly established.

McCrea¹ investigated this subject most intensively from the experimental standpoint. He concluded that the commonly accepted view that the left vagus is distributed to the anterior surface of the stomach and the right to the posterior is incorrect, as each supplies fibers to both surfaces. The vagus nerve possesses both accelerator and inhibitor fibers, but is largely accelerator in its function. He pointed out that resection of both vagi in the neck proves fatal, while section of one vagus or one splanchnic nerve is without effect. McCrea further asserted that vagal section results in dilatation, diminished tonus, decreased peristalsis and delayed emptying of the stomach. Splanchnic section, on the other hand, has the reverse effect. The section of all nerves gives results similar but somewhat less marked than vagal section alone. According to this observer, these results are not permanent, but following a period of time the tonus is restored, and peristalsis becomes normal. He considered it doubtful whether any actual permanent influence, either on secretion or on acidity, is produced.

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* From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland

¹ McCrea, E. D'A. Brit J Surg **13** 621 (April) 1926

Psychic and reflex secretion disappears on vagal section, and although the secretory curve is altered, acid juice still continues to be secreted.

Attention may be directed to other experimental work on the resection of the vagi recorded by various observers. Lorenzi² reported his results of resection of these nerves, either in the neck or below the diaphragm in rabbits. He noted that hemorrhages were frequently produced in the mucous membrane of the stomach, and that in some instances hemorrhagic erosions developed. Saitta³ was able to produce multiple ulcers in certain rabbits following bilateral vagotomy after the administration of a 3 per cent solution of muriatic acid. Yzeran⁴ severed both vagi below the diaphragm in twenty rabbits and succeeded in producing chronic ulcers in the pyloric region of the stomach in ten. In 1906, Cannon⁵ observed as a result of severing the vagi bilaterally below the origin of the recurrent laryngeal nerve, a disturbance of the motor function of the stomach, at first, but recovery occurred within a few days.

Ophuls⁶ resected both vagi below the diaphragm and produced gastric ulceration in six of eighteen rabbits in twenty-four days. He observed but slight changes in the gastric secretion. In Auer's⁷ experiments in which both nerves were resected in the neck in rabbits, death quickly ensued. By severing both nerves below the diaphragm, gastric ulcers were produced in some instances. Portis and Portis⁸ produced a true achylia by means of a subtotal gastrectomy in dogs. Whether this was due, however, to removal of a nerve center located at the incisura is considered doubtful. Hughson⁹ observed a diminution in the normal emptying time of the stomach in dogs following resection of the vagus nerves. Klein¹⁰ reported his results in eight cases of duodenal ulceration associated with marked hyperacidity in which partial gastrectomy was performed. In but one quarter of these cases could an anacid state be obtained. In eight cases, however, in which in addition section of the left vagus was performed, anacidity occurred in all. Hartzell¹¹ observed that following section of the vagus nerve in

2 Lorenzi *Rassegna de sc med* **8** 313, 1893

3 Saitta *Gaz d osp* **21** 599, 1900

4 Yzeran *Ztschr f klin Med* **43** 181, 1901

5 Cannon *Am J Physiol* **17** 429, 1906-1907

6 Ophuls *J Exper Med* **8** 181, 1906

7 Auer *Am J Physiol* **25** 334, 1909-1910

8 Portis, B, and Portis, S. A. Effect of Subtotal Gastrectomy on Gastric Secretion. Experimental Study by Aid of Pavlov Pouch in Dogs, *J A M A* **86** 836 (March 20) 1926

9 Hughson, W. Effect of Vagus Neurotomy on Pyloric Sphincter. Experimental Study, *J A M A* **88** 1072 (April 2) 1927

10 Klein, E. *Ann Surg* **90** 65, 1929

11 Hartzell, J. B. *Am J Physiol* **91** 161, 1929

the neck, changes in the gastric secretion occurred in the form of a reduction of both free hydrochloric acid and total acidity. In those animals, however, in which the branches of the vagus were sectioned in the abdomen a normal secretion of free hydrochloric acid was occasionally noted.

Burkle-de-la Camp¹² was able to bring about, by means of subcutaneous injections of histamine, a flow of gastric juice of such high acidity as to produce peptic ulcerations in rats. This occurred even following division of both vagi. Pieri and Tanferna¹³ performed in six of nine persons with recurring ulcers, supradiaphragmatic resection of the left vagus, while in the other three bilateral resection was made under the diaphragm. He observed a lowering of the hydrochloric acid and of the pepsin. Later, however, both the hydrochloric acid and pepsin content rose steadily and in some instances regained and even exceeded the previous figures. Thompson¹⁴ likewise found that bilateral vagotomy lowered the gastric secretion in the pylorotomized stomach of the dog. He also pointed out, on the other hand, the fact that following this operation meals of ordinary size may contain sufficient protein to neutralize all of the hydrochloric acid that the fundus is capable of secreting.

Winkelstein¹⁵ called attention to the effect of vagus section in establishing a reduction in the gastric acidity following partial gastrectomy for ulcer. Berg¹⁶ likewise reported his results following the division of the left pneumogastric nerve, which he performs regularly in all patients who have high acidities prior to subtotal gastrectomy in the treatment for ulcer. He found that these patients become anacid in from two weeks to several months following section of the left vagus nerve.

EXPERIMENTAL WORK

As considerable doubt still remains as to the permanent effect of vagal section on gastric secretion, it was considered of sufficient importance to investigate this problem further. This work was greatly facilitated by the operative aid given us by Dr. Alfred Ullman and Dr. Ferdinand A. Ries.

Twenty-two dogs were utilized in these experiments. Healthy adult dogs of medium size were selected for the purpose. Psychic influences were eliminated as far as possible by allowing the dogs to become familiar with their laboratory environment for some time. Repeated

12 Burkle-de-la Camp. *Deutsche Ztschr. f. Chir.* **220** 31, 1929.

13 Pieri, G., and Tanferna, U. *Riforma med.* **46** 323, 1930.

14 Thompson. *Proc. Staff Meet., Mayo Clin.* **5** 88, 1930.

15 Winkelstein, A. *Am. J. Surg.* **7** 494, 1929.

16 Berg, A. A. *Ann. Surg.* **92** 340, 1930.

analyses were made before operation to accustom the animals to the use of the tube. The following methods of obtaining the gastric contents were utilized:

1 Fifty cubic centimeters of 7 per cent solution of alcohol was introduced into the fasting stomach through a tube, and the contents were extracted in forty minutes.

2 One and a half milligrams of histamine (ergamine acid phosphate) was injected subcutaneously during the fasting state, and the

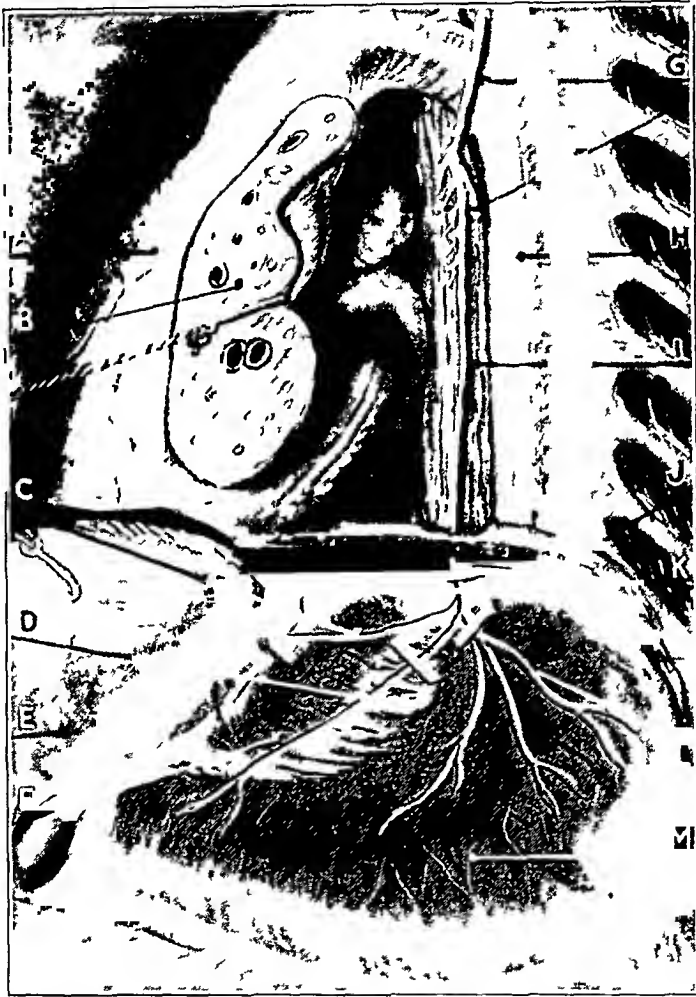


Fig 1—Drawing illustrating the distribution of the main gastric branches of the left vagus nerve. The nerve was severed at the three points indicated by the black cross-line. *A* indicates the heart, *B*, the cut surface of the left lung, *C*, the hepatic branch, *D*, the anterior nerve, *E*, the lesser curvature of the liver, *F*, the omentum minus, *G*, the left vagus nerve, *H*, the aorta, thoracalis, *I*, the gastric secretion in a dog in which the vagus nerve was severed below the diaphragm, *L*, anterior gastric branches, and *M*, the stomach.

contents of the stomach were extracted in thirty minutes. Weekly or biweekly extractions were performed regularly on each animal.

These secretions were examined for free hydrochloric acid and total acidity according to the usual method. The utilization of test meals

containing food as is ordinarily practiced for obtaining gastric contents has been found unsatisfactory in animals whereas the alcohol and histamine stimulation has proved to be far more trustworthy

After the normal findings were definitely established, the vagus nerve was severed, as will be later described. Frequent gastric analyses were again performed, and the results compared with those obtained from the normal animal. It was deemed best in order that these comparisons could be properly evaluated that an average be obtained. This was accomplished by averaging the results of numerous test meals obtained before and following operation.

In nine dogs, following the alcohol test meal, the normal average of hydrochloric acid was 22 and the total acidity 46. With the histamine

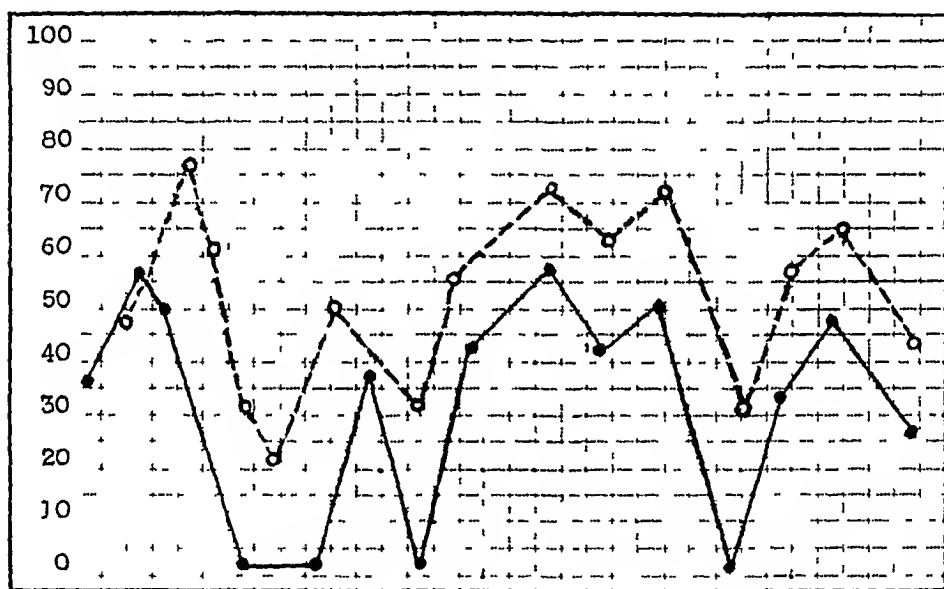


Fig 2—Chart illustrating the free hydrochloric acid and total acidity of the gastric secretion in a dog in which the vagus nerve was severed below the diaphragm. The irregularity of the acid curve, noted after fifteen weekly extractions, following histamine stimulation, is shown. Free acid is indicated by the solid line, total acid, by the broken line.

test, in ten dogs the normal average free hydrochloric acid was 65 and the total acidity 94.

It is important to note that the continued use of histamine as a stimulant to the gastric secretion was at no time followed by any ill effect, nor were there any lesions produced in the stomach as the result of this drug. The quantity of gastric contents obtained from animals after severance of the nerve differed in no way from that secured from the normal.

Following a thorough study of the normal gastric secretion in each dog the vagus nerve and its branches were severed at various locations, under strict aseptic precautions. At each operation at least one half

an inch of the nerve was resected, and histologic studies were then made of this portion in order that there could be no doubt as to the removal of nerve tissue. Following operation, all of the dogs lost weight for a short period, which they gradually regained, with the exception of the group to be later described. During the entire period of the experiments, ranging from three to twelve months, the dogs were placed on the usual laboratory diet with the exception of the group just mentioned. Following the first two weeks most of the animals apparently enjoyed good health and suffered no ill effects as the result of the operation.

Roentgenologic studies were also made in order to determine whether delay in emptying of the stomach was produced by vagal section.

In the first group of ten dogs, the left vagus nerve was severed at a location just below the diaphragm. All of the animals showed a steady tendency to progressive loss of flesh with marked weakness, and unless placed under special dietetic regimen, died in a short time. In three of the ten dogs death followed quickly, and at autopsy acute peritonitis with free pus in the abdominal cavity was revealed. In three others, convulsive seizures developed before death. Four dogs were placed on a milk diet and increased in weight. They survived for a period of three months in an apparently healthy state, then they were killed. In these dogs, following histamine stimulation the gastric content showed an average free hydrochloric acid of 63 and a total acidity of 80, indicating that there was but a slight change produced in the secretions as compared with that noted before the operation.

In a second group of three dogs the anterior branch of the left vagus nerve was severed. These dogs lived nine months and were then killed. The average free hydrochloric acid following the alcohol test meal was 25, the total acid, 43. After stimulation with histamine, the average free hydrochloric acid was 36, the total acidity, 53. The results of the alcohol test meal compared closely with that observed in the normal, while those following histamine stimulation showed a marked decrease in the free hydrochloric acid and total acidity.

In a third group of two dogs the principal anterior branch of the left vagus nerve was severed, one dog died three weeks following the operation. The second dog, observed over a period of five and a half months, revealed an average free hydrochloric acid content of 16 and a total acidity of 42 following the alcohol test meal, and an average free hydrochloric acid of 55 and a total of 70 following the histamine stimulation. This experiment showed a slight decrease in the gastric acidity as compared with the normal.

In a fourth group of two dogs, the left vagus nerve was severed in the neck. These dogs were observed over a period of ten months. The free hydrochloric acid of the gastric secretion averaged 29 and the total acidity 46 with the alcohol test, following histamine stimulation, the free

hydrochloric acid averaged 39 and the total acidity, 55. It is evident that no marked changes were observed following the alcohol test meal, while the histamine test showed a marked diminution in both the free acid and the total acidity.

In a final group of two dogs, the right vagus nerve was severed in the neck, just below the recurrent laryngeal branch. The dogs were observed over a period of six and a half months. The average obtained following the alcohol test meal revealed a free hydrochloric acid of 18 and a total acidity of 38. The histamine stimulation showed an average free hydrochloric acid of 70 and total acidity of 81. These findings differ markedly from those obtained following the severance of the left vagus nerve in the neck, in that they compare more closely with the results obtained in the average normal.

It is of interest to state that the roentgenologic examination made in eight dogs following the vagal section revealed no delay in the emptying time of the stomach in the six hour study. At this period the stomach was found to be empty and the barium observed only in the terminal ileum and colon. In most instances the colon was only partially filled and a considerable amount of the opaque meal had been evacuated, indicating a hypermotility of the gastro-intestinal tract.

Complete autopsies were performed following death in all of the dogs in order to demonstrate that the proper nerve had been sectioned. The esophagus, stomach and duodenum were carefully investigated, and no lesions were detected in any instance. The mucous membrane of the stomach appeared normal, and there was no evidence of dilatation.

CONCLUSIONS

From these experiments the following conclusions may be drawn:

1. Section of the left vagus nerve immediately below the diaphragm produces but a negligible change in the gastric secretion as compared with the normal.
2. Following section of the anterior gastric branch of the left vagus nerve the acidity may remain either normal or become markedly decreased.
3. Section of the principal anterior branch of the left vagus is followed by slight decrease in the gastric acidity.
4. After section of the left vagus in the neck the secretion continues to be normal or there results a marked diminution in the acidity.
5. Following section of the right vagus nerve, the findings vary but slightly from the normal.
6. It is therefore evident that while at times changes in the gastric secretion occur owing to section of the vagus nerve these are inconstant, there is likewise a general tendency for this secretion to return to normal when diminished as the result of this operation.

THE EFFECT OF BRONCHIAL ASTHMA ON THE CIRCULATION^{*}

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The pathologic physiology of bronchial asthma is manifested by an edema of the mucous membranes and a spasm of the smooth muscle of the bronchi and bronchioles. The air passages become closed, and owing to this closure there is subsequent difficulty in breathing, particularly in expiration. As a result of prolonged and frequent attacks of this type of dyspnea, the lungs become distended and emphysema supervenes. In the latter condition, the alveoli are distended, causing a flattening of the alveolar wall with consequent narrowing, tearing and even destruction of the capillaries, which results in diminution of alveolar circulation and increased pressure within the pulmonary arteries. Theoretically, this should result in increased work for the right ventricle.

This assumption seems to be borne out by Kahn,¹ who concluded from an electrocardiographic study of fifty cases of bronchial asthma that the majority of his patients demonstrated a state of hypertrophy of the right ventricle. This conclusion is based on the finding of right ventricular preponderance present in only one fifth of the entire series—a finding that he took to be identical with right ventricular hypertrophy. In a more recent report, Unger² went a step further and concluded from an electrocardiographic study of seventy-four cases of bronchial asthma that there was evidence of actual cardiac damage in his patients, as shown by the presence of mild conduction disturbances, right ventricular preponderance and a tendency toward such preponderance. The only other report on the subject is by Alexander, Luten and Kountz,³ who, as a result of a painstaking and thorough study of

^{*} Submitted for publication, May 14, 1931.

^{*} From the Department of Internal Medicine and the Clinic of Applied Immunology, University of Pittsburgh.

^{*} Read before the Society for the Study of Allergy and Allied Conditions, Atlantic City, May 2, 1931.

1 Kahn, M. H. Electrocardiogram in Bronchial Asthma, *Am. J. M. Sc.* **173** 555 (April) 1927.

2 Unger, L. Heart in Bronchial Asthma, Electrocardiographic Study of Seventy-Four Cases, *J. Allergy* **2** 17 (Nov.) 1930.

3 Alexander, H. L., Luten, D., and Kountz, W. B. Effect on the Heart of Long Standing Bronchial Asthma, *J. A. M. A.* **88** 882 (March 19) 1927.

fifty patients, found, unlike the observers quoted, that bronchial asthma has no deleterious effect on the heart

Two questions therefore present themselves in this connection
Do repeated attacks of bronchial asthma produce cardiac damage?
What is the state of the heart during an acute and severe paroxysm?

TABLE 1—*The Heart*

Case	Age	Weight	Duration, Years	Family History	Associated Allergy	Skin Tests	Foci			Im physema	Cardiac Etiology	Symptoms
							Sinu sitis	Tonsils	Teeth			
1	42	180	20	Neg	Negative	Pos	Neg	Pos	Neg	Present	None	None
2	14	78	5	Neg	Negative	Pos	Pos	Pos	Neg	Absent	None	None
3	26	136	16	Pos	Negative	Pos	Pos	Out	Neg	Present	None	None
4	11	58	9	Pos	Negative	Pos	Pos	Out	Neg	Present	Scarlet fever	None
5	18	122	5	Neg	Negative	Pos	Neg	Neg	Pos	Present	None	None
6	40	149	7	Neg	Urticaria	Pos	Pos	Pos	Neg	Present	None	None
7	12	67	5	Neg	Negative	Pos	Neg	Neg	Neg	Present	None	None
8	22	96	16	Neg	Hay fever	Pos	Pos	Neg	Pos	Present	None	None
9	55	150	6	Pos	Negative	Pos	Neg	Neg	Neg	Absent	Rheumatic fever	None
10	67	112	16	Neg	Negative	Pos	Pos	Pos	Pos	Present	None	None
11	29	140	25	Pos	Negative	Pos	Pos	Out	Out	Present	None	None
12	14	115	10	Neg	Negative	Pos	Neg	Neg	Neg	Present	None	None
13	44	119	7	Neg	Negative	Pos	Pos	Neg	Neg	Present	None	None
14	37	104	16	Pos	Negative	Pos	Neg	Neg	Neg	Present	None	None
15	47	154	14	Neg	Negative	Pos	Neg	Neg	Neg	Present	None	None
16	50	169	5	Neg	Negative	Pos	Pos	Pos	Neg	Present	None	None
17	54	144	14	Pos	Urticaria	Pos	Pos	Neg	Neg	Present	None	None
18	56	101	36	Pos	Urticaria	Pos	Pos	Neg	Neg	Present	None	None
19	40	88	7	Pos	Hay fever	Pos	Pos	Neg	Neg	Present	None	None
20	21	133	6	Neg	Negative	Pos	Neg	Pos	Neg	Present	None	None
21	37	140	7	Neg	Hay fever	Pos	Neg	Pos	Neg	Present	None	None
22	34	117	6	Neg	Hay fever	Pos	Neg	Neg	Neg	Present	None	None
23	26	134	14	Pos	Negative	Pos	Neg	Pos	Neg	Present	None	None
24	32	170	11	Pos	Negative	Pos	Neg	Neg	Pos	Present	None	None
25	32	170	8	Pos	Hay fever urticaria	Pos	Neg	Pos	Neg	Present	Rheumatism	None
26	50	180	11	Pos	Negative	Pos	Neg	Out	Neg	Present	Rheumatism	None
27	31	202	5	Neg	Negative	Pos	Neg	Neg	Neg	Present	Rheumatism	None
28	21	85	12	Pos	Eczema	Pos	Neg	Neg	Neg	Present	Rheumatism	None
29	57	137	5	Neg	Negative	Pos	Neg	Pos	Neg	Present	Rheumatism	None
30	25	115	20	Pos	Hay fever	Pos	Pos	Neg	Neg	Present	Rheumatism	None
31	38	208	8	Neg	Urticaria	Pos	Pos	Pos	Neg	Present	Rheumatism	None
32	38	165	27	Neg	Rhinitis	Pos	Pos	Pos	Pos	Present	Rheumatism	None
33	6	40	5	Pos	Negative	Pos	Neg	Out	Neg	Present	Rheumatism	None
34	11	78	10	Pos	Negative	Pos	Neg	Out	Neg	Present	Rheumatism	None
35	57	137	15	Pos	Negative	Pos	Pos	Neg	Neg	Present	Rheumatism	None
36	43	130	20	Neg	Negative	Pos	Neg	Out	Neg	Present	Rheumatism	None
37	46	145	7	Neg	Negative	Pos	Neg	Out	Pos	Present	Rheumatism	None
38	42	132	15	Pos	Negative	Pos	Neg	Neg	Neg	Present	Rheumatism	None
39	67	126	20	Pos	Negative	Pos	Neg	Neg	Neg	Present	Rheumatism	None
40	43	187	9	Neg	Negative	Pos	Neg	Neg	Neg	Present	Rheumatism	None
41	29	129	21	Pos	Hay fever	Pos	Neg	Out	Pos	Present	Rheumatism	None
42	23	124	6	Pos	Negative	Pos	Neg	Out	Neg	Absent	Rheumatism	None
43	23	110	5	Pos	Negative	Pos	Pos	Neg	Neg	Absent	Rheumatism	None
44	51	181	42	Pos	Negative	Pos	Neg	Pos	Pos	Present	Rheumatism	None
45	25	115	22	Pos	Negative	Pos	Pos	Neg	Neg	Absent	Rheumatism	None
46	48	162	30	Pos	Negative	Pos	Pos	Out	Neg	Present	Rheumatism	None
47	8	45	7	Pos	Negative	Pos	Neg	Pos	Neg	Absent	None	None
48	40	168	6	Pos	Negative	Pos	Pos	Neg	Neg	Present	None	None
49	43	176	40	Pos	Hay fever	Pos	Pos	Out	Neg	Present	None	None
50	43	158	5	Pos	Negative	Pos	Pos	Pos	Pos	Absent	None	None

* The abbreviations occurring in table 1 are explained thus: M R stands for the transverse diameter of the L D the long diameter, S A equals sinus arrhythmia, L V P equals left ventricle preponderance, and R A P.

EFFECT OF REPEATED ATTACKS OF BRONCHIAL ASTHMA ON THE HEART

For the purpose of this study a series of fifty consecutive cases of bronchial asthma was used. This material was obtained both from the clinic and from private practice. Only the following patients were

in Bronchial Asthma²

Rate	Blood Pressure		Murmur	Effort Test	Ventricular Pressure		X Ray (6 ft)				Vital Capacity	Electrocardiograms	
	Sys tolie	Dias tolie			Between Attacks	During Attacks	M R	M L	Tr	L D		Between Attacks	During Attacks
84	130	90	Funet	Good	70		50	106	156	155	71	S A, L V P	
90	120	70	None	Good	65		30	62	92	110	101	L V P	
84	118	80	None	Good	75		44	63	107	117	70	S A, L V P	L V P latent block
90	100	65	None	Good	80	90	27	55	82	90	56	S A, R V P	
80	90	60	None	Good	65		36	57	95	95	42	Normal	
80	100	70	None	Good	70		41	90	131	145	76	S A	
82	95	56	None	Good	65	105	29	65	94	100	89	R V P	
86	110	85	None	Slight limit	60	105	38	61	99	106	92	L V P	P B of right V source
88	140	90	None	Good	55		30	98	128	151	90	L V P	
87	100	60	None	Slight limit	60		35	82	117	123	70	S A	
78	100	70	None	Good	80	90	41	75	116	125	49	Normal	
100	110	80	None	Good	75		33	65	98	112	55	S A, L V P	
77	100	65	None	Limit	55	80	36	82	118	127	74	S A	
96	100	80	None	Good	60	85	37	71	108	125	80	S A	
84	135	80	None	Good	65		42	82	125	140	92	S A, L V P	
84	135	75	None	Good	70	90	45	76	128	121	62	Normal	Normal
90	164	100	None	Good	75							Normal	
88	120	60	None	Good	85							Normal	
90	115	85	None	Good	70							Normal	
80	100	70	None	Good	53		40	75	115	125	52	S A, L V P	
80	120	69	None	Good	64						68	Normal	Normal
80	100	62	None	Good			35	85	120	130	73	Normal	
84	110	68	None	Good							101	Normal	
80	115	70	None	Good	55	95	46	70	116	125	59	Normal	Normal
94	154	80	Mitral	Slight limit	60	104	40	80	120	130	65	R V P	
54	110	65	None	Good	70		45	65	110	115	78	S A, L V P and bradycardia	
82	150	80	None	Good	55						78	S A	
86	105	65	None	Good	50						68	L V P	
90	148	83	None	Good							72	S A	
84	110	50	Funet	Good	65		37	73	110	125	54	Normal	Normal
94	170	80	Funet	Good	70		55	90	145	145	56	Normal	
90	140	63	None	Good	75		40	80	120	125	79	S A	
84	70	40	None	Good	60						89	Normal	Normal
85	100	52	None	Slight limit	65						86	Normal	Normal
80	108	70	None	Good	65		40	65	105	120	73	S A	
88	140	74	None	Good	70	85	35	70	105	130		S A	
90	140	75	None	Good	80						64	Normal	
86	138	68	None	Good	65						65	Normal	
80	130	70	None	Good	54						73	S A	
82	160	72	None	Good	58						67	P B	
78	100	50	None	Good	59		45	60	105	110		S A	
76	120	60	None	Good	65		40	70	110	115		Normal	
84	105	80	None	Good	64		35	75	110	120	53	S A	
76	120	70	None	Good	58		50	81	131	135	49	S A	
82	110	50	None	Good	62		35	70	105	120	76	S A	
88	145	80	Mitral	Good	60		40	60	100	110		R V P	
92	83	56	None	Good	50							Normal	
82	130	64	None	Good	70		41	78	119	126		Normal	
80	120	65	None	Good	50		45	82	127	135		Normal	
87	128	64	None	Good	75		40	85	125	130		Normal	

heart to the right of the midline, and M L that to the left of the midline, Tr is the total transverse diameter, and right ventricle preponderance, P B equals premature beats, and V equals ventricular

included those who gave an unmistakable history of paroxysmal seizures and asthmatic symptoms, those who gave a personal history of some additional allergic manifestation, such as hay fever or hives and a positive familial history, and those who gave positive skin tests to either the inhalant or ingestant group of proteins. No patient was included whose history of attacks did not cover a period of at least five years. The distribution of the patients in this group with regard to the duration of their illness may be seen in table 2 and fig 1. There were twenty in whom the duration of the condition was between five and ten years, and nine who had been ill for from ten to fifteen years

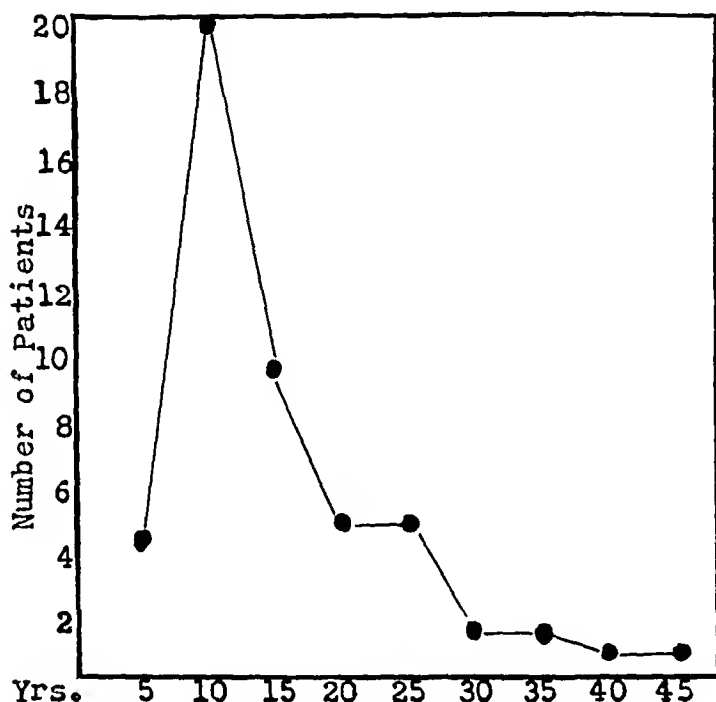


Fig 1—Graph of the number of patients and duration of illness

Table 2 and fig 2 show the distribution of patients with reference to age. Thirty-four of the fifty patients were from 20 to 50 years of age. Of the entire group, sixteen presented no evidence of foci of infection in the tonsils, teeth or sinuses. Twenty-three had infected sinuses, fourteen showed diseased tonsils, and nine presented some evidence of apical infection in the teeth (table 3).

These patients were subjected to a thorough clinical and laboratory cardiac investigation. The clinical survey comprises a cardiac history and physical examination. The laboratory data consist of vital capacity and venous pressure determination, electrocardiographic tracings and complete cardiac measurements obtained from roentgenograms of the chest taken at a distance of 6 feet (183 cm). These studies were

carried on during the asthma-free period, and show the following results. Two of the patients had rheumatic mitral disease, a condition that was independent of, and anteceded, their asthma. Two more

TABLE 2—*Findings in Bronchial Asthma*

Age of Patients			Duration		
Years	Number	Per Cent	Years	Number	Per Cent
5-10	2	4	5	5	10
10-20	6	12	5-10	20	40
20-30	12	24	10-15	9	18
30-40	11	22	15-20	5	10
40-50	11	22	20-25	5	10
50-60	6	12	25-30	2	4
60-70	2	4	30-35	2	4
			35-40	1	2
			40-45	1	2

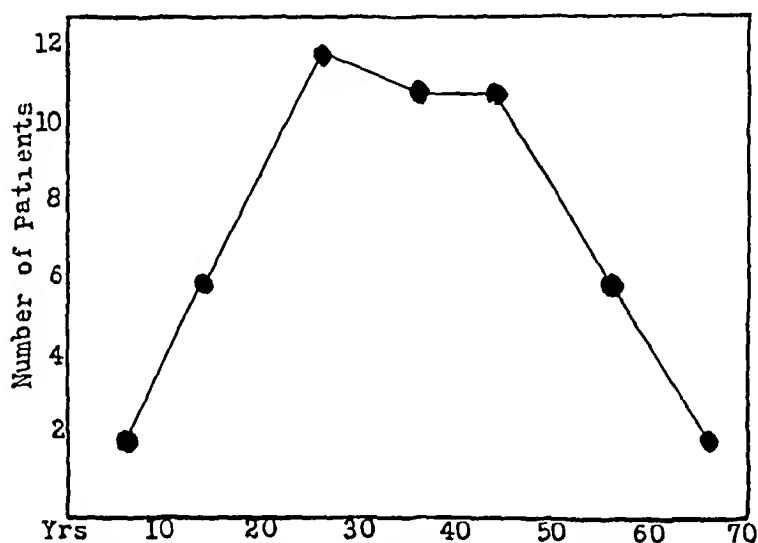


Fig 2—Graph of the distribution of the disease according to the age of the patients

presented apical systolic murmurs which were definitely functional. Four patients showed some restriction in their response to effort, both as regards increasing fatigue and abnormal reaction of pulse and blood pressure following such exercise as walking up one flight of steps. The rest of the cardiac examination, however, did not indicate the presence of cardiac damage. As seen in table 1, hypotension was almost the rule in the entire group. What its underlying mechanism was does not seem entirely clear. It is certain, however, that it was not due to myocardial damage, but that it might be due to possible involvement of the autonomic nervous system. The majority of the patients showed a reduction in vital capacity that ranged from 49 to 100 per cent of the normal, with an average reduction of 61 per cent for the group.

(table 3 and fig 3) The calculations are made according to the tables of West and Meyers⁴ The diminution in vital capacity in all likelihood was due to the presence of emphysema, for in only seven of the

TABLE 3—Findings in Bronchial Asthma

Vital Capacity			Focus of Infection		
Reading, per Cent	Number	Per Cent	Source	Number	Per Cent
40- 50	3	7.5	Tonsils	14	28
50- 60	7	18	Teeth	9	18
60- 70	7	18	Sinuses	23	46
70- 80	13	34	None	16	32
80- 90	4	10			
90-100	3	7.5			
100-1.0	2	5			

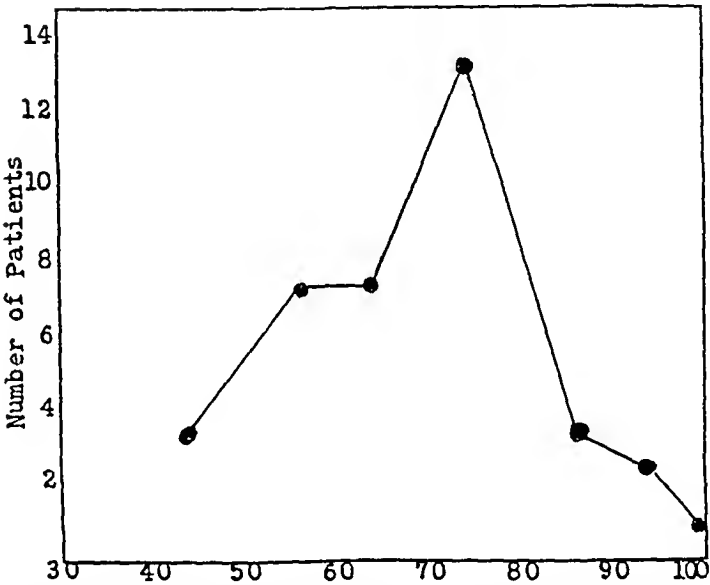


Fig 3—Graph of the vital capacity of patients with bronchial asthma

fifty patients was emphysema entirely absent. The venous pressure as determined by the indirect method during the asthma-free period was well within normal, ranging from 5.5 cm to 8 cm of water. It showed, however, a tendency to rise during the acute paroxysm (table 1).

In the interpretation of electrocardiograms, a tracing is considered normal if it shows no evidence of arrhythmia, if the P-R (auriculo-ventricular) interval does not exceed 0.2 second, if there is no preponderance of the right or left ventricle, and if there is no abnormality of the various representatives, particularly the T wave, an abnormality that so frequently denotes myocardial or coronary disease. It

⁴ Meyers, J. A. Vital Capacity of the Lungs, Baltimore, Williams & Wilkins Company, 1925.

is interesting to note that of the entire series, 42 per cent showed mild grades of sinus arrhythmia (tables 1 and 4, and fig 4) The incidence of this finding was apparently independent of the age of the patient

TABLE 4—*Electrocardiogram in Bronchial Asthma*

Duration, Years	Electrocardiogram					
	Normal	S A	L V P	R V P	Cond	Myoc
5-10	12	8	5	2	P B 1	0
10-20	5	7	5	1	0	0
20-30	1	5	0	1	0	0
30-40	1	1	0	0	0	0
40-50	2	0	0	0	0	0
Total	21	21	10	4	1	0

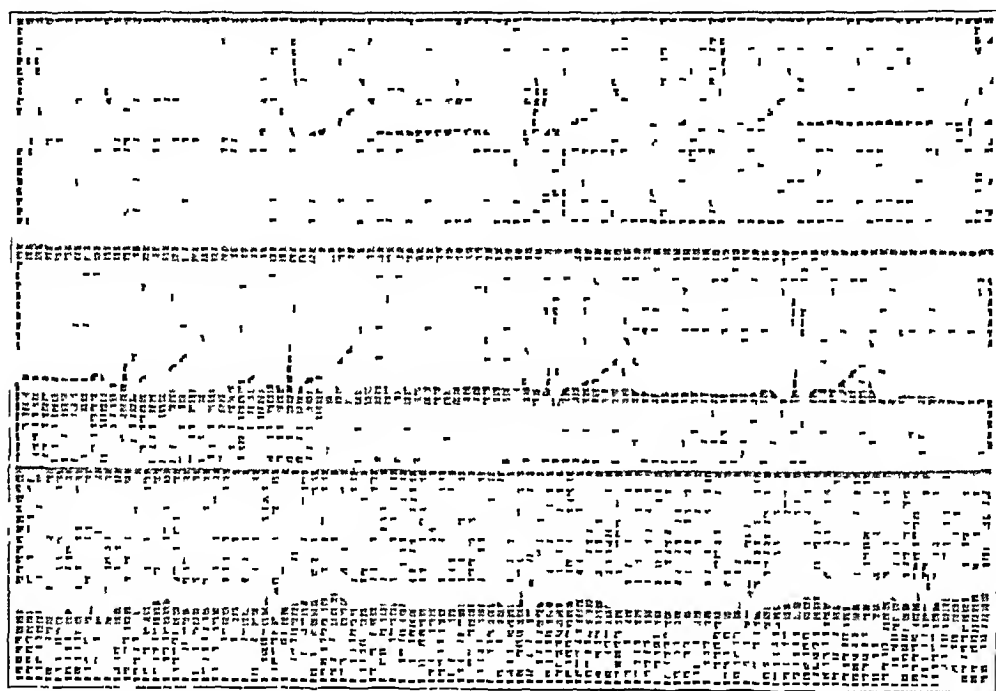


Fig 4 (case 13) —Marked sinus arrhythmia, vagus effect, three leads

Ten patients, or 20 per cent, showed left ventricular preponderance, and four patients, or 8 per cent, showed right ventricular preponderance. However, of these four patients, two had mitral disease, and right ventricular preponderance is not an uncommon finding in this condition. Occasional premature beats of ventricular origin were found in one instance. The rest of the series, twenty-one patients or 42 per cent, presented entirely normal tracings. It should be noted that this percentage would be more than doubled if sinus arrhythmia and ventricular preponderance were not considered abnormal. Sinus arrhythmia in these cases was due to the vagotonia with which bronchial asthma is so frequently associated. This vagus effect is shown particularly in case 26 which presents the electrocardiographic picture of

sinus arrhythmia, left ventricular preponderance and a marked bradycardia, with a rate of 40 (fig 5) The clinical significance of ventricular preponderance is apparently not very great As an isolated finding, it is not infrequently seen in normal persons, and presents itself as a result of numerous factors other than cardiac impairment As a matter of fact, while it was thought originally that preponderance of a ventricle is synonymous with increase in ventricular muscle mass, and that preponderance is a fairly reliable means of estimating the relative weight of the ventricles, this view has undergone some modification It is shown that the position of the heart in the chest is a determining factor, and more recently Fahr,⁵ and Herman and

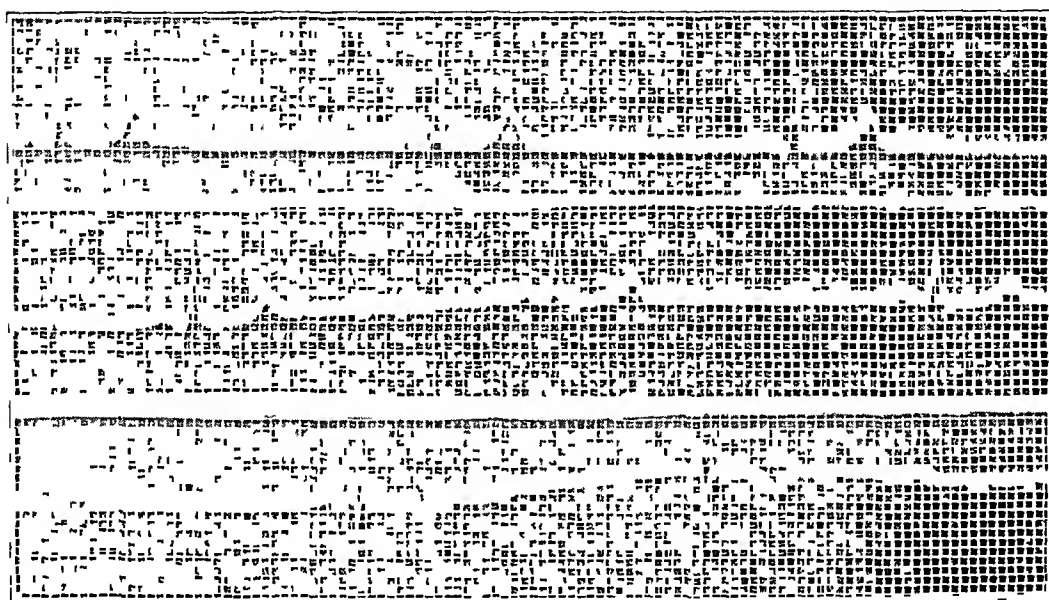


Fig 5 (case 26) —Sinus arrhythmia, bradycardia, left ventricular preponderance

Wilson⁶ showed that the picture of preponderance may be affected by the propagation of the impulses through, and the anatomic distribution of the conduction system, that what is now considered right preponderance may be left preponderance, and vice versa To substantiate this view, Barker and his co-workers⁷ presented fairly definite evidence by showing that what is now interpreted as premature beats of left ventricular origin is obtained experimentally in the human heart by stimu-

5 Fahr, G Some Fundamental Principles of Electrocardiography, Arch Int Med **27** 126 (Jan) 1921

6 Herman, G R, and Wilson, F N Ventricular Hypertrophy, Heart **9** 91 1922

7 Barker, P S, Macleod, A G, and Alexander, J The Excitatory Process in Exposed Human Heart, Am Heart J **5** 720 (Aug) 1930

lating directly the right ventricle. If the latter views are correct, and there is reason to believe they may be so, the significance of the finding of right ventricular preponderance in bronchial asthma by Kahn and Unger is difficult to evaluate. In view of these considerations, and in view of the fact that preponderance is seen relatively so frequently in apparently normal persons, it appears that ventricular preponderance, per se, bears no important clinical significance in bronchial asthma and certainly does not indicate either cardiac strain or cardiac damage.

The cardiac measurements are taken from roentgenograms of the chest made at a distance of 6 feet in order to demonstrate any possible enlargement of the heart and particularly of the right side of the heart.

These measurements are compared with standard normal measurements for sex, height and weight, according to the tables of Claytor and Merrill, as quoted by Vaquez.⁸ With the exception of only four patients who showed a slight increase in the transverse diameter, the cardiac measurements of the series studied are found to be well within the normal limits.

It is thus seen that patients with bronchial asthma exhibit neither symptoms nor physical findings suggestive of organic heart disease. On the laboratory side, there are no vital capacity, venous pressure, electrocardiographic or roentgenologic changes to suggest cardiac damage or heart failure. Furthermore, the literature affords no evidence of pathologic changes in the hearts of asthmatic patients who came to autopsy.⁹

THE HEART DURING THE ACUTE ASTHMATIC ATTACK

Since the symptoms of bronchial asthma are due to mild asphyxia, and since patients who die of an attack die of acute asphyxia, it is logical to expect that functional cardiac changes might occur during the acute attack that would be less extensive but nevertheless comparable to those seen in lower animals dying of anaphylaxis. Anaphylaxis when fatal in the guinea-pig is due to asphyxia which results, very much as in bronchial asthma, from closure of the bronchi and bronchioles so that expiration is not possible. I reported¹⁰ that electro-

8 Vaquez, H. and Bordet, E. *The Heart and the Aorta*, New Haven, Yale University Press, 1920, pp. 28-29.

9 Kountz, W. B., and Alexander, H. L. Death from Bronchial Asthma, Three Cases, *Arch. Path.* **5** 1003 (June) 1928. Pollack, M. Bronchial Asthma with Case Reports and Post Mortem Records, *U. S. Vet. Bur. M. Bull.* **4** 214 (March) 1928. Rackemann, F. M. Fatal Asthma. Report of Case with Autopsy, *Boston M. & S. J.* **194** 531 (March 25) 1926. Huber, H. L., and Koessler, K. K. The Pathology of Bronchial Asthma, *Arch. Int. Med.* **30** 689 (Dec.) 1922.

10 Crip, Leo H. Electrocardiographic Studies of Effect of Anaphylaxis on the Cardiac Mechanism, *Arch. Int. Med.* **48** 1098 (Dec.) 1931.

cardiograms taken of guinea-pigs in a state of fatal anaphylactic shock demonstrate profound changes in cardiac rhythm and conduction, changes that range from simple acceleration of rate, delayed conduction and various degrees of heart block to ventricular fibrillation and cardiac standstill. Many of the tracings show inversion of the T wave in lead 1 and 2, and are suggestive of the picture seen in coronary occlusion. These changes are not specific of anaphylaxis, as they occur also if asphyxia is artificially induced by clamping off the trachea. The conclusion is therefore reached that they are due chiefly to myocardial anoxemia.

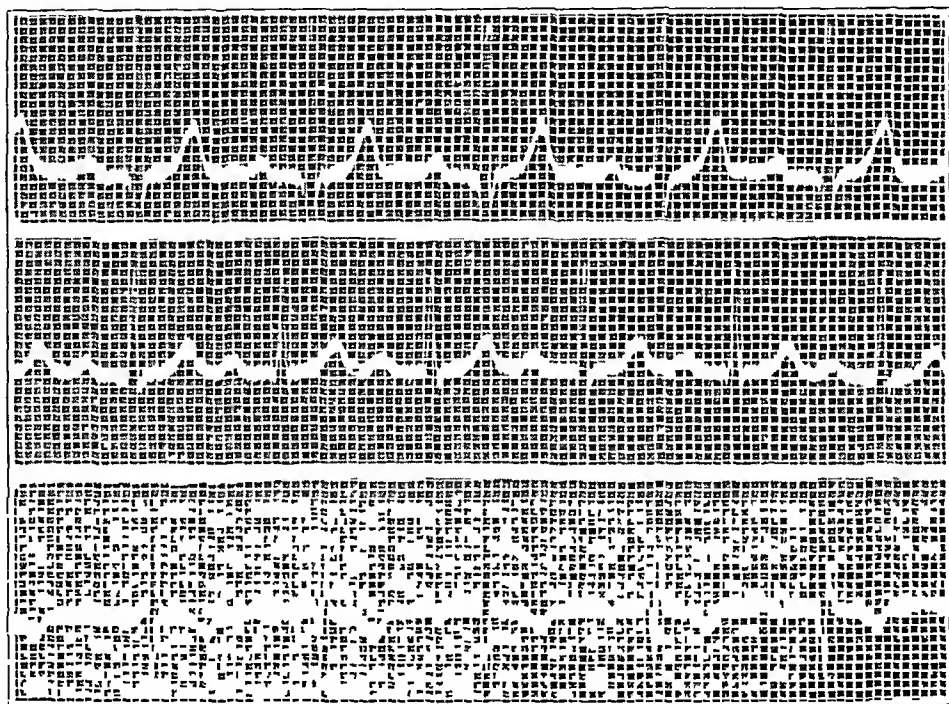


Fig 6 (case 3) —Delays in A-V conduction during asthmatic attack. P-R interval, 0.24 second, three leads.

In order to demonstrate the effect of the acute asthmatic attack on the heart, twenty cases are reported. Of these, electrocardiograms were available in eight, while in twelve careful note was made of the pulse as regards its rate and rhythm. In the latter group, one patient showed clinically premature beats which occurred throughout the attack and for several hours following it. The other eleven patients showed no arrhythmia. Of the eight patients of whom electrocardiograms were made during the paroxysm (table 1), six were normal and two presented definite functional disturbances. One of these, case 3, showed definite delay in auriculoventricular conduction (fig 6). This patient was a young adult the duration of whose asthma was sixteen years. An electrocardiogram taken during the asthma-free period showed only left

ventricular preponderance and normal conduction time. The tracing shown in figure 6, taken during a prolonged and severe attack, shows a P-R interval of 0.24 seconds, and this finding continued to be present for several days following the cessation of the acute symptoms.

The second patient, case 8, was a man, aged 22, who had had asthma since childhood. He also had hay fever, being highly sensitive to ragweed, and a very serious constitutional reaction developed ten minutes following treatment with ragweed extract. This reaction was characterized by urticaria, hay fever, asthma seizure and signs and

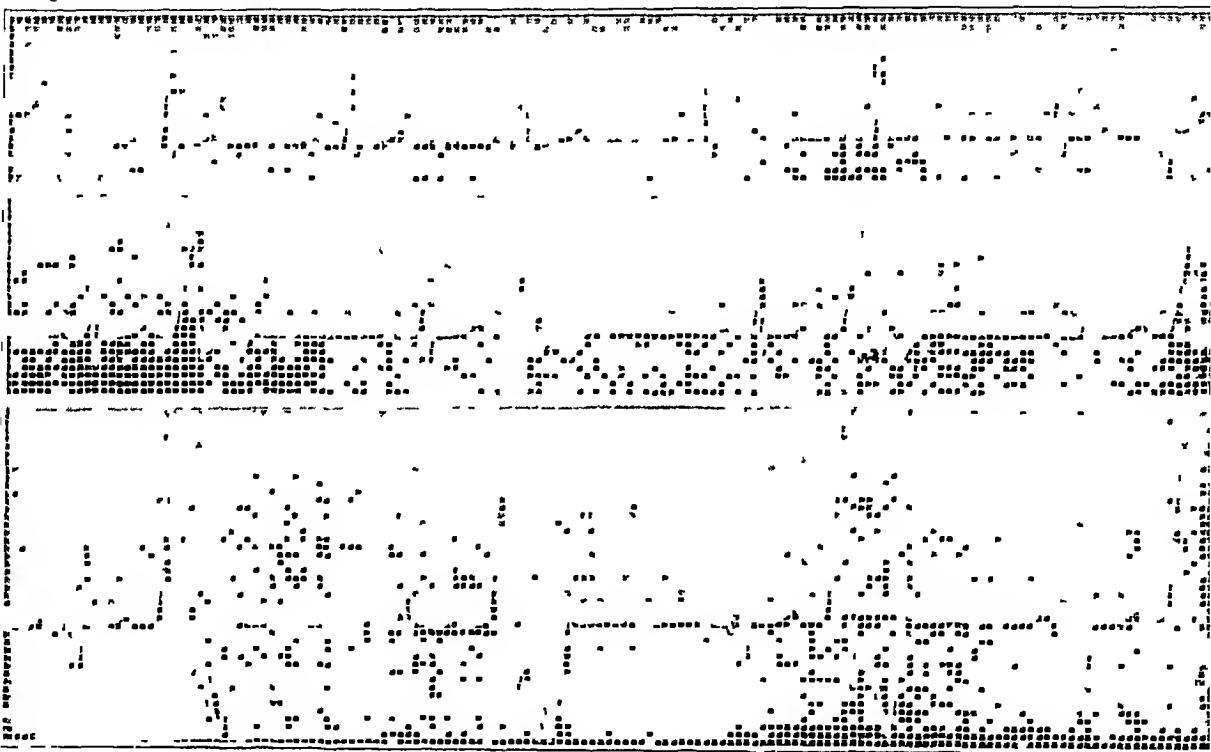


Fig 7 (case 8) —Electrocardiogram taken during severe constitutional reaction. Mild sinus arrhythmia, premature beats of right ventricular origin, left ventricular predominance.

symptoms of suffocation and circulatory failure. An electrocardiogram obtained at this time (fig 7) showed an occasional premature beat in lead 1, followed by premature beats of right ventricular origin occurring regularly after every other normal beat. This patient received 0.4 cc of epinephrine hydrochloride fifteen minutes previous to the taking of the electrocardiogram, but it is unlikely that the epinephrine hydrochloride was responsible for these findings, the drug did not produce premature beats in other asthmatic patients, and at least one patient on whom a report is made in this paper showed premature beats before he received epinephrine hydrochloride.

It is true that the changes shown by both of these patients were very slight. At the same time, they were definite and seemed to be more or less directly connected with, if not actually caused by, the asphyxia of the asthmatic attack. The more advanced disturbances of rhythm that are observed in anaphylaxis and asphyxia in lower animals are not seen in clinical asthma, because the process is not sufficiently severe in the human being to cause such an analogously profound asphyxia. On the basis, however, of the foregoing findings, the opinion is ventured that electrocardiographic studies in fatal cases of asthma would show cardiac changes similar to those in fatal anaphylaxis.

SUMMARY

1 A complete cardiovascular survey of fifty patients suffering from bronchial asthma is presented.

2 An electrocardiographic study of the acute asthmatic attack in eight patients is reported.

CONCLUSIONS

1 Bronchial asthma does not have a permanent damaging effect on the cardiovascular system.

2 Acute attacks may as a result of the associated asphyxia produce minor transitory disturbances in cardiac conduction.

1004 May Building

PSITTACOSIS

WITH RESULTS OF POSTMORTEM EXAMINATION IN A
CASE INCLUDING STUDIES OF THE SPINAL CORD^{*}

S H POLAYES, M D

AND

M LEDERER, M D

BROOKLYN

The following case is reported, firstly, because as far as could be ascertained it is the first case of psittacosis in New York City in which the diagnosis was confirmed both by bacteriologic and by postmortem examination, and secondly, because the case permitted of studies on the changes in the spinal cord

REPORT OF CASE

B H, aged 51, a white woman, Jewish, a housewife, was admitted to the Jewish Hospital of Brooklyn to the private service of Dr Meyer Rabinowitz on Feb 5, 1931. The chief complaints were chills and fever for the last two days and pain in the back for the last four days.

Present Illness—About a week before admission the patient was seized with intermittent chills. A physician was called and diagnosed her condition as "grip." The following day the patient felt improved, but three days later she developed signs of pneumonia and was taken to the hospital.

History—The history was unimportant except for dyspnea on exertion. A brother died of "pneumonia" the previous week at the age of 65.

Physical Examination—The patient lay quietly in bed and presented a definite malar flush and cyanosis of the lips and fingertips. The temperature was 105 F. The pulse rate was 116, and the respirations numbered 60 per minute. The blood pressure was 140 systolic and 70 diastolic. The pupils were equal and contracted, and failed to react to light. The ears, nose, throat and cervical lymph nodes were normal.

Examination of the chest showed limitation of expansion, dulness on percussion and moist râles over both bases, with tubular breathing above these areas. The patient did not complain of any chest pain. The heart showed no changes other than a rough systolic murmur at the apex.

The abdomen was moderately distended. On the day of admission the patient had five bowel movements. (The diarrhea persisted throughout her illness.)

February 6. The patient developed a hacking cough without expectoration, but was moderately comfortable in an oxygen tent. Respirations were mainly abdominal and at the rate of 30 per minute. Cyanosis persisted. The pulse rate was 112 (occasionally irregular), and respirations numbered 27 per minute. The temperature fluctuated between 104 and 105.8 F, and the blood pressure was 166 systolic and 70 diastolic. There was still absence of pleuritic pain.

* Submitted for publication, April 25, 1931.

* From the Department of Pathology, the Jewish Hospital.

February 7 A pleural rub over the right anterior part of the chest was heard for the first time. Crepitant rales were heard over the upper left and entire right side of the chest posteriorly up to the apex, while over the lower lobe of the left lung there was now more resonance, indicating a regression of the process below with extension to the apex.

It may be of interest to note that the changes indicating a progressive ascending process from base to apex has been observed previously and referred to by Peterson as a creeping pneumonia.

February 8 No appreciable change in condition was noted.

February 9 The patient showed a definite decline. The pulse was irregular, the abdomen was distended, the respirations were shallow and rapid and the cyanosis was more marked. The patient became delirious and showed marked twitching of the face and extremities.

In the afternoon of the same day a reappearance of crepitant râles was noted over the base of the left lung, apparently a secondary infection. Numerous fine rales were also heard over the entire right side of the chest. The occasional hacking cough persisted, but remained unproductive.

February 10 The delirious state and abdominal distention were more severe, and the patient expelled large amounts of watery and foul fecal matter. Repeated examinations of the stool for blood and parasites gave negative results.

February 14 A spinal tap was performed, and 15 cc of opalescent fluid under pressure was removed.

February 16 The abdominal distention increased, and the bowel movements continued foul and watery. The cyanosis became more marked and the respirations were very rapid (50 per minute) and labored, becoming gasping in character. The pulse became imperceptible, and death occurred at 9 a. m.

About five days after the patient's admission to the hospital the following information was obtained. Her brother (B¹) and his neighbor (F) had recently returned from Havana with six parrots. One of these parrots died on board the ship. The neighbor took the dead parrot and one of the live ones home with him. Shortly afterward, however, the second parrot also died. Of the remaining four birds, a pair (male and female) were taken by each of the patient's two brothers (B¹, B²). The male bird of one and the female of the other of these two pairs flew away and the older (B²) of the two brothers took the remaining two birds for mating purposes. He soon became ill and died of "pneumonia" (now believed to be of psittacosis origin) five days after the onset of the disease. One of the birds of the remaining pair also became ill and died during the course of its owner's illness. Then in rapid succession each of the following persons became ill: the sister (H) of B², whose case is here reported, two of his daughters (S and G) and the wife of his brother, who originally brought the birds from Havana and who for a time shared one of the birds of the last pair. They all had been at the home and had attended the funeral of the first victim. All were admitted to the hospital and all recovered except the patient whose case was just described. Two of the survivors (S, Mrs. B¹) had an uncomplicated course while the third (G) was still in the hospital at the time of this writing, recovering from the effects of a pulmonary embolus complicating convalescence.

Laboratory Data—The urine showed traces of albumin and occasional red and white blood cells. Study of the blood revealed red cells, 4,490,000, with 0.5 per cent reticulation, white cells, 10,800, polymorphonuclear neutrophils, 86.5 per cent, with 45 per cent nonsegmented forms, lymphocytes, 11 per cent, monocytes, 1.5 per cent, neutrophilic myelocytes, 0.5 per cent, metamyelocytes, 0.5 per cent,

platelets, 150,000 per cubic millimeter, hemoglobin, 64 per cent (Dare), color index, 0.7 per cent, bleeding time, 10 seconds, and coagulation time, 10 minutes. Repeated examination gave similar results. Blood taken for culture on February 6 was reported sterile after three days' incubation. The spinal fluid was under increased pressure and opalescent owing to the presence of numerous red blood cells. Albumin and globulin were present. Fehling's solution was reduced. The Wassermann test was negative. Colloidal gold was not reduced.

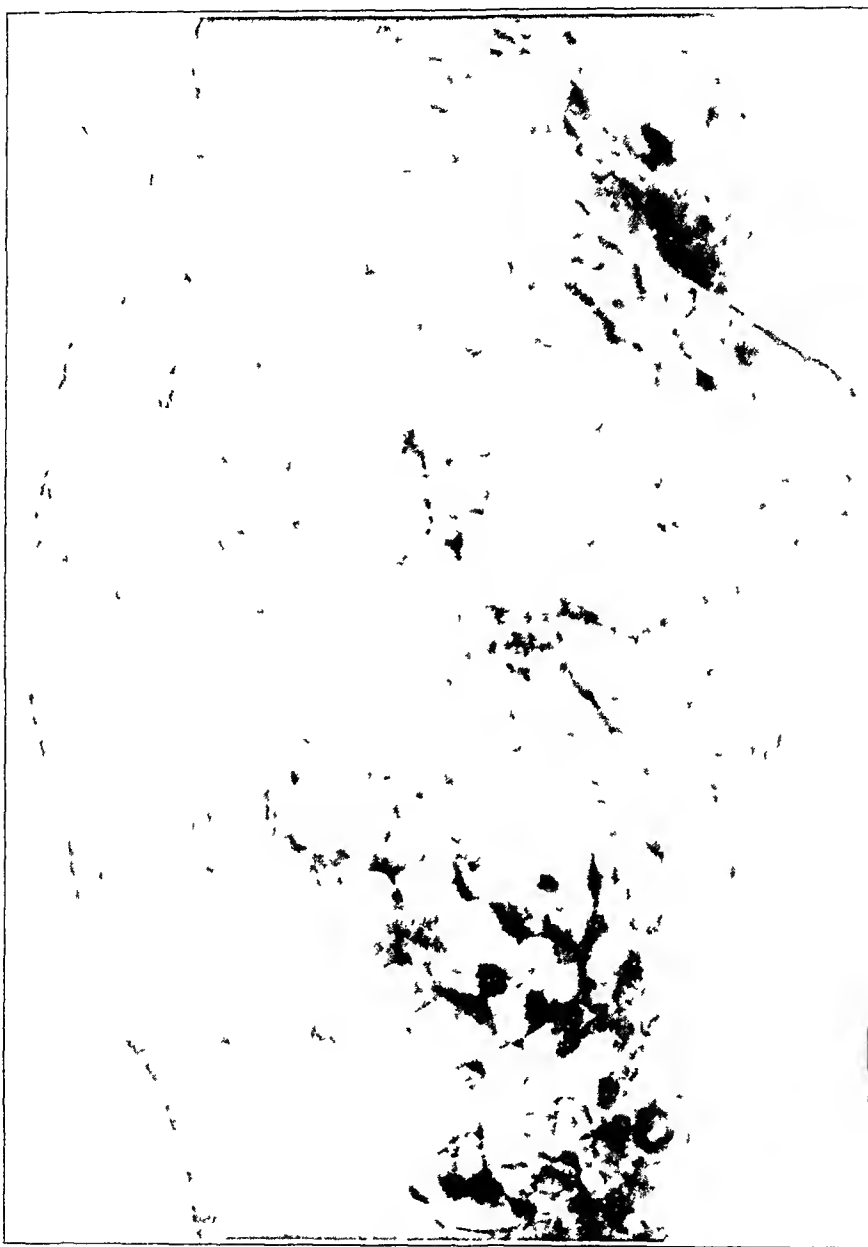


Fig 1—Surface of consolidated lung showing the typical smooth pleura

Autopsy—The body was that of an obese white woman. The external appearance showed nothing remarkable. The skin and mucous membranes showed no changes. The panniculus was thick. The muscles were bluish red and well developed.

Cavities In the peritoneal cavity firm adhesions bound the transverse colon to the gallbladder. The pleural and pericardial cavities were normal.

The macroscopic examination showed certain conditions. Larynx. There was edema of the entire submucosa. Hemorrhagic areas were found in the epiglottis and just below the vocal cords. Trachea. Changes similar to those noted in the larynx were observed. Bronchi. The larger bronchi showed changes similar to those in the trachea.

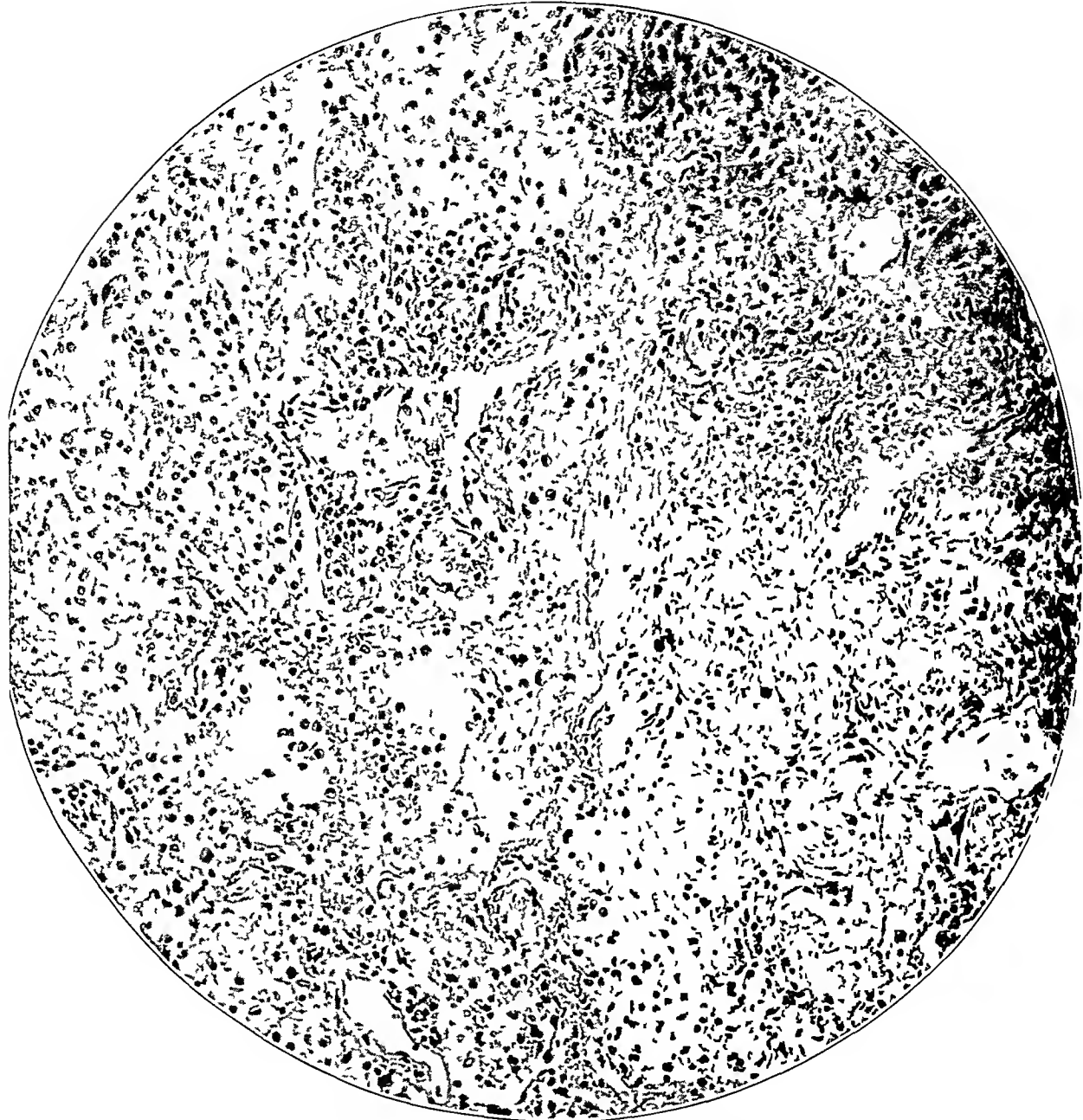


Fig 2—Section through the red area of consolidation showing fine and coarse fibrinous deposits in the alveoli and interalveolar septums, reduced from a magnification of 90.

Microscopic changes were also seen. Larynx. Congestion and edema were noted in the submucosa. Mononuclear, plasma and a few polymorphonuclear neutrophilic cells infiltrated this area. A thick layer of fibrin separated the zone of infiltration from the stroma beneath it. Trachea. Congestion and extravasation of blood

beneath the mucosa were observed. This process was accompanied by an infiltration with numerous polymorphonuclear, plasma and small as well as large mononuclear cells, the latter predominating. Bronchi. Examination of the right bronchus showed a marked congestion of the vessels throughout the entire depth of the wall. The latter was the seat of an infiltration similar to that noted in the trachea. Small

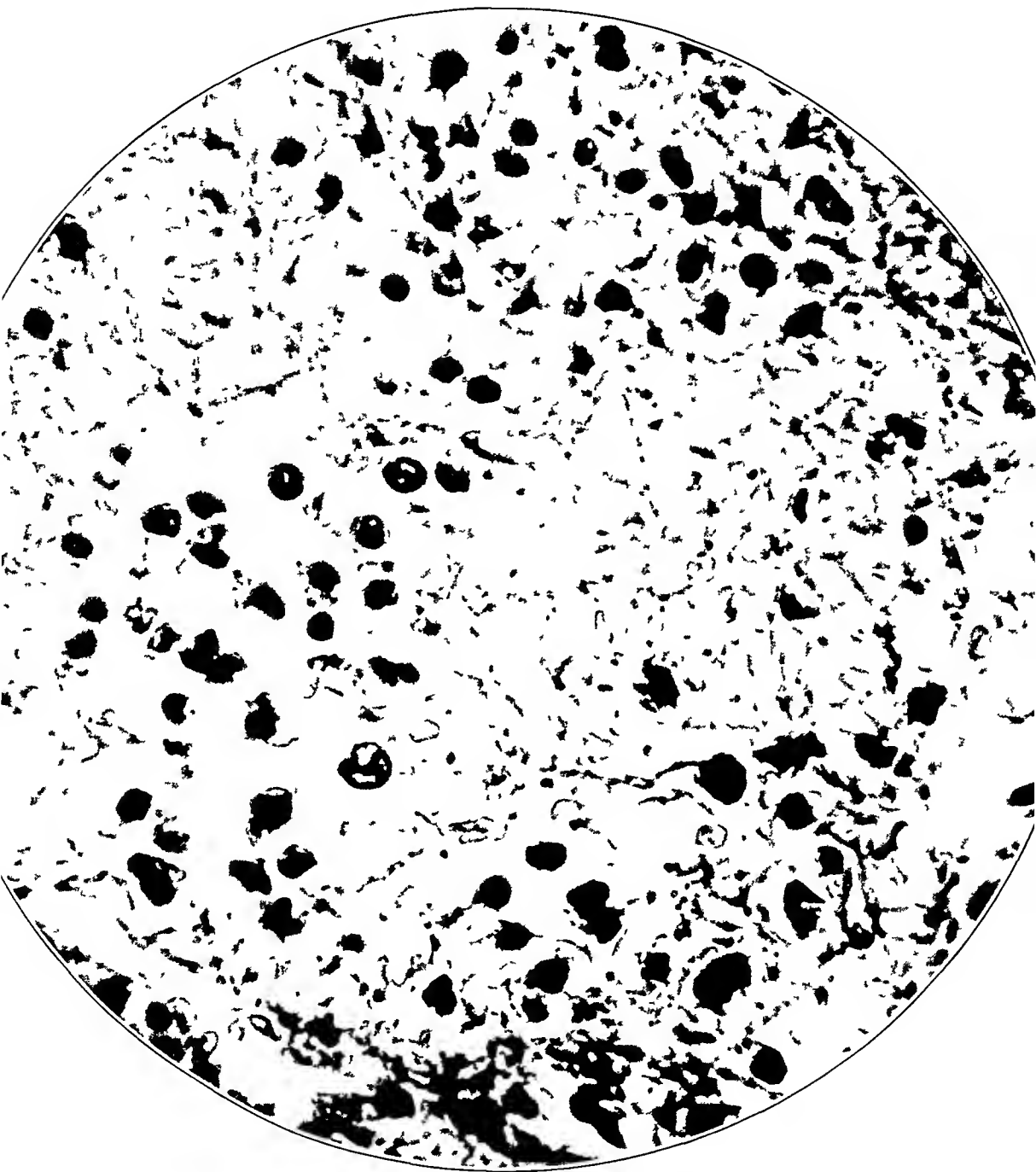


Fig. 3—High power field showing the typical alveolar exudate consisting of large mononuclear cells, desquamated cells of the alveolar lining and plasma cells enmeshed in a fine fibrinous network. Polymorphonuclear leukocytes are absent.

mononuclear cells infiltrated the surrounding lung parenchyma. The left bronchus showed a similar but less marked involvement. The peribronchial lymph nodes were fibrosed and filled with anthracotic deposits. Numerous phagocytic cells and plasma cells were found diffusely infiltrating the interstices of the node.

Lungs The right upper lobe was voluminous, firm in consistency throughout and bluish red, and had a smooth pleural surface (fig 1) Section showed a uniformly dense, glossy, grayish-blue parenchyma Microscopic examination revealed marked congestion and edema of the alveolar walls The interalveolar septums in some sections were thickened by a fibrinous network which extended into the alveolar spaces This was quite striking In many alveoli it was made up of extremely fine fibrils forming a very delicate intertwining network In others, the deposit was quite thick with only a few cells enmeshed in it (fig 2) In most of the alveoli of this section there were found many plasma cells and



Fig 4—Cut surface of consolidated lung showing areas of consolidation and large thrombi in the pulmonary arteries

large mononuclear cells, some of which had apparently been actively engaged in phagocytosis Desquamated cells of the alveolar lining and large, pale vacuolated cells simulating ring forms were also scattered throughout the fibrinous network in the alveoli Polymorphonuclear leukocytes were extremely scarce, and in many sections entirely absent The alveolar epithelium was markedly hypertrophied and proliferative (fig 3)

The right middle lobe showed similar parenchymal changes and, in addition, presented numerous thrombi plugging the blood vessels (fig 4) Microscopic examination showed the bronchial walls to be markedly infiltrated with mononuclear and plasma cells The alveoli showed changes similar to those already noted, and many of the pulmonary vessels were plugged by platelet thrombi The epithelia

of the bronchial mucosae were almost entirely desquamated. The arteries showed markedly thickened medial coats. Many of the capillaries contained hyaline thrombi.

The right lower lobe macroscopically showed a more intensely red discoloration, although here also the bluish-gray patches were found occupying large areas of pulmonary parenchyma. Microscopic examination of the tissue showed a more pronounced hemorrhagic infiltration of alveoli as well as of alveolar septums.

The left upper lobe showed old adhesions which obliterated the interlobar fissure. Cut section showed irregular gray raised rough patches, some discrete and others conglomerated, scattered throughout the parenchyma. The larger patches were situated near the interlobar adhesions. Microscopic examination showed a process similar to that described in the right lung.

The left lower lobe showed similar but less extensive involvement. Microscopic examination showed changes essentially like those already noted, except for more abundant fibrin deposits in the involved alveoli. Areas of emphysema were found in the superficial portions of all lobes.

The left main pulmonary artery contained a large gray thrombus which was not adherent to the vessel wall and which on microscopic examination showed the typical architecture of a platelet thrombus. The smaller pulmonary arteries also contained gray thrombi.

Cardiovascular System. The heart weighed 380 Gm. The epicardium was normal, and the myocardium edematous. The left ventricular myocardium was markedly hypertrophied. The mitral valve consisted of three leaflets, the accessory one being about one-half the size of the other two. Hemorrhagic areas were found in the endocardium of the mitral, tricuspid and aortic leaflets. The foramen ovale was partially patent. The coronary arteries were normal. Microscopic examination showed swelling of the muscle cells throughout. Sections through the posterior wall of the left ventricle showed small discrete foci of polymorphonuclear and plasma cell infiltration between muscle cells. The tricuspid valve in the region of the hemorrhagic area noted on gross examination was the seat of a subendocardial extravasation of red cells. The middle aortic cusp showed a marked subendocardial fibrin deposit.

The aorta and other large arteries showed a moderate atherosclerosis macroscopically and microscopically.

The right iliac vein was occluded by a gray thrombus, not adherent to the vessel. Microscopic examination of the vein showed a typical platelet thrombus with no change in the vessel wall. Numerous cocci were found in the thrombus.

Gastro-Intestinal Tract. The entire wall of the esophagus was edematous and the mucosa was the seat of areas of marked congestion. Microscopic examination showed markedly congested vessels beneath the mucosa with an infiltration by plasma cells and occasional large mononuclear cells.

The cardiac portion of the stomach mucosa was extremely hemorrhagic. The pyloric portion was polypoid and less hemorrhagic. Microscopic examination showed extravasation of blood in the mucosa of the cardia and congestion of the entire submucosa.

There were numerous mucosal hemorrhages in the small as well as the large intestines. Dense adhesions bound the ascending colon to the gallbladder. The lymph follicles of the intestines showed no changes. Microscopic examination showed no abnormalities other than congestion of the vessels and occasional areas of infiltration with large mononuclear cells.

Biliary Tract. The liver weighed 2,550 Gm. The capsule was smooth and glistening. The consistency was firm. The color was pale reddish brown with

yellow mottling. The architecture was clouded. The main portal vein was normal, but its right branch was reduced to a fibrous cord, containing no visible lumen. The left branch was of large caliber, and as it entered the deeper portion of the parenchyma it gave off branches to the right lobe. Section through the right lobe of the liver through the altered right branch of the portal vein showed the tissue in that region to be the seat of a gray scar. One of the smaller vessels passing through this area contained a thrombus, apparently of recent origin. The biliary channels were normal. The hepatic veins were normal. The bed of the gallbladder was the seat of dense adhesions that bound the organ to the under surface of the liver. Microscopic examination showed a marked fat replacement with only a few small areas of normal liver parenchyma. The distribution of the fatty changes was central as well as periportal. This was accompanied by a periportal small round cell infiltration. There was also a marked bile pigment deposit in many of the liver cells. Section through the scar showed platelet thrombi in the large branches of the portal vein. The liver tissue in this region was completely replaced by a scar, and the surrounding hepatic parenchyma was markedly replaced by fat.

The gallbladder was embedded in a mass of adhesions which bound it to the hepatic flexure of the colon. The wall of the organ was markedly thickened and pearl gray. Its lumen was occluded by several large bile pigment calculi. The rugae of the mucosa were hypertrophied, and in areas adhered to each other to form separate pockets containing inspissated bile. The cystic duct was normal except for a thickening of its wall. Microscopic examination showed a marked fibrosis of the organ.

The pancreas weighed 100 Gm. It was firm in consistency and on section, the head of the organ presented a small pearl-gray discrete nodule. Microscopic examination revealed a pronounced interstitial fibrosis. The nodule was found to consist of a large island of dark-staining epithelial cells, irregularly scattered although some of them showed a tendency to alveolar and ductlike structure. This nodule was completely circumscribed by a dense fibrous capsule.

The spleen weighed 400 Gm. The capsule was smooth. The color was reddish purple and the consistency extremely soft. Cut section showed a semifluid jelly-like splenic parenchyma. The splenic vein was occluded by a large gray thrombus which was unattached to the vessel wall. Microscopic examination showed a marked extravasation of blood in the pulp throughout the organ. Scattered throughout the parenchyma were found numerous large mononuclear and plasma cells. The splenic follicles were obscured by the hemorrhagic process and reduced in size and number. The venous sinuses were engorged with blood and pigment. The arteriolar walls were thickened.

Each suprarenal gland weighed about 10 Gm. In both organs there was cloudy swelling and the medullary portions showed softening and red discoloration. Microscopic examination showed a marked autolysis of the parenchyma and congestion of the medulla in each organ.

Genito-Urinary System. The left kidney weighed 250 Gm, the right, 275 Gm. The capsules stripped with slight difficulty, leaving a rough bluish-gray surface with numerous cortical cysts of varying size. On the surface of the left kidney there was a small stellate scar. Section through the organ showed a cloudy swelling of the parenchyma. The larger vessels showed thickening of their walls. The pelves were markedly hemorrhagic and edematous. Microscopic examination showed congestion of the glomerular tufts and slight granular degeneration of the tubular epithelium. The pelvis was edematous and the seat of marked extravasations of blood. The stellate cortical scar noted in the left kidney was the seat

of an infiltration with mononuclear cells and a marked fibrosis that replaced the glomeruli and tubules of the involved portion of kidney

The ureters were normal. The bladder was normal except for edema of its wall.

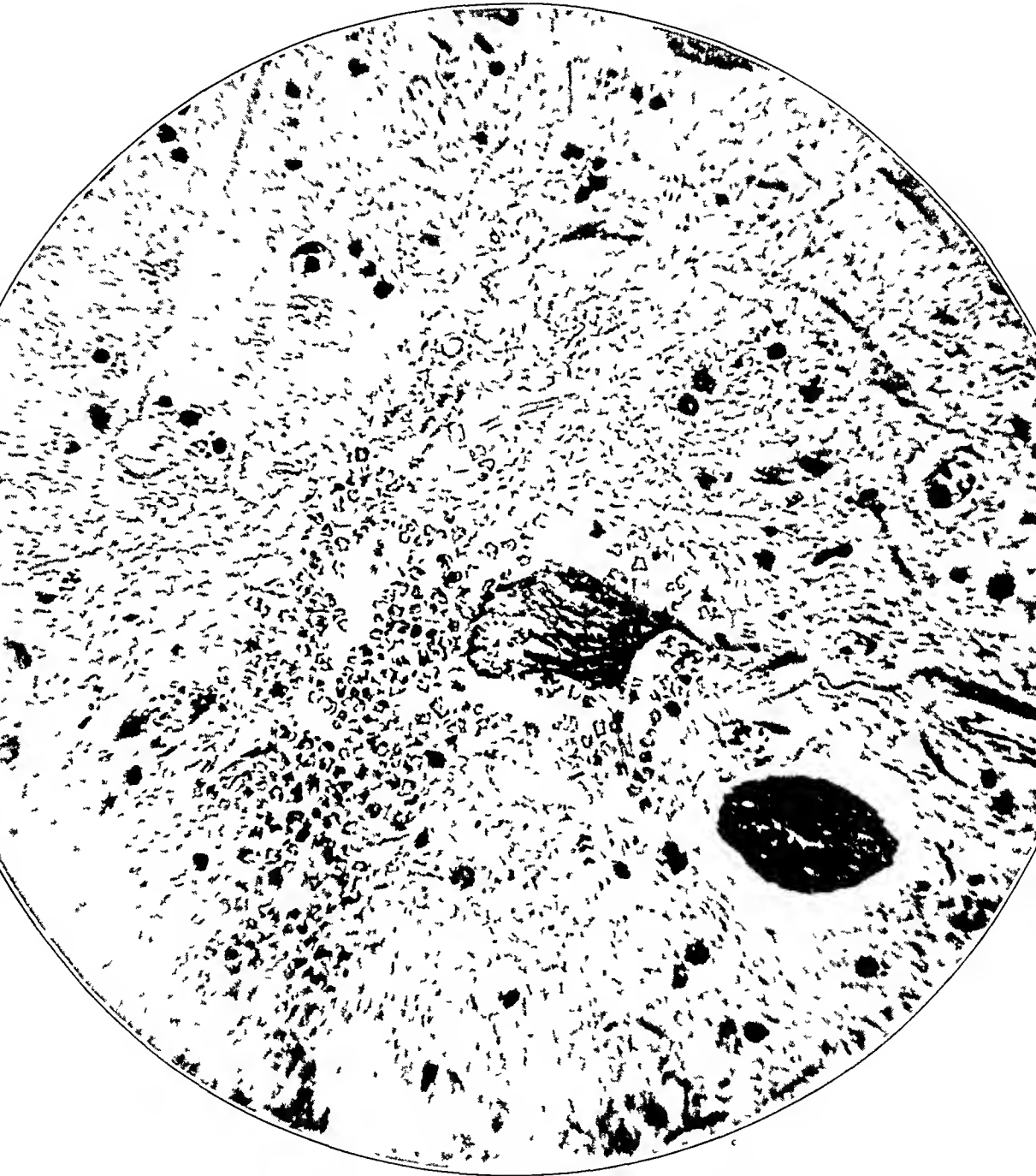


Fig 5—High power field in anterior horn of the spinal cord showing changes in the morphology of the neurons and hemorrhages

The uterus was the seat of intramural and subserous fibroids. The endometrium was hemorrhagic and polypoid. Microscopic examination showed a marked polypoid hyperplasia of the endometrium and cystic changes of the glands of the cervical mucosa. The fibroids in the wall of the uterus presented areas of cystic degeneration. The fallopian tubes showed congestion on gross and microscopic examination. The ovaries were slightly enlarged and the seat of small

cysts, some of which contained clear yellow fluid, others, bloody fluid. Microscopic examination showed follicular cysts, some filled with extravasated blood.

Thyroid The left lobe was the seat of a thick-walled cyst. The right lobe was normal. Microscopic examination revealed the presence of a fetal adenoma and a cystic degeneration of the left lobe. The right lobe was normal.

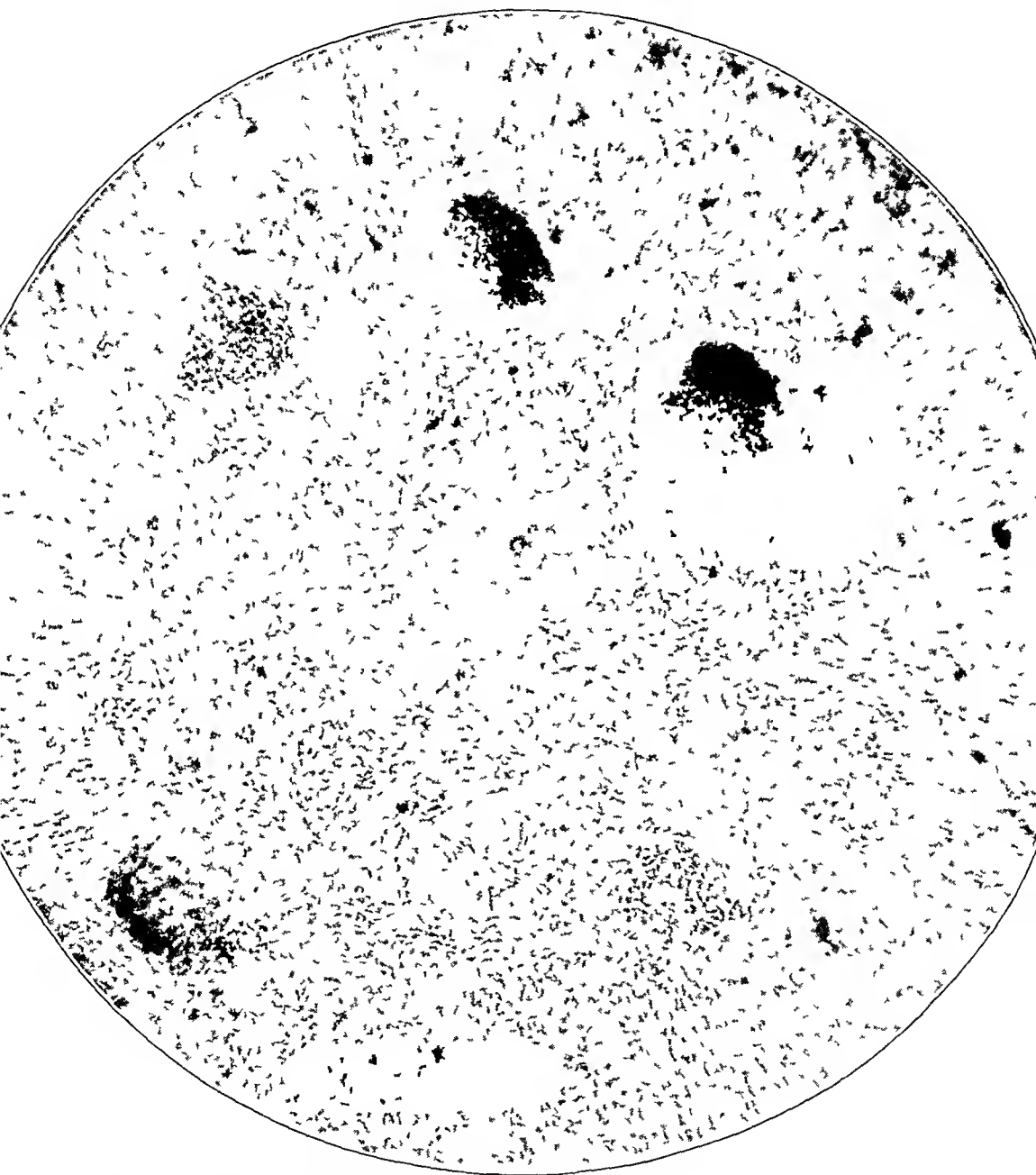


Fig 6—High power field of anterior horn of the spinal cord, showing fat droplets in neurons, sudan III

Thymus This was almost completely replaced by fat. Microscopic examination showed almost complete replacement of the thymic structure by fat and lymphocytes.

Ribs and Vertebrae These were normal. The rib marrow was red and on microscopic examination showed a hyperplasia of all elements.

Examination of the brain was not permitted.

Spinal Cord The dura mater was moderately congested. The pia mater, especially in the region of the lumbar segments, showed a more marked congestion of vessels. Transverse section of the spinal cord revealed a yellowish discoloration of the right posterior horn. Microscopic examination of celloidin and paraffin preparations with various stains showed the following. With hematoxylin and eosin stain there was a moderate amount of chromatolysis of the anterior horn cells and an increase in the glial cells. Some of the neurons showed other morphologic changes, consisting of a transformation of the usual pyramidal form into rounded or otherwise distorted shapes and an eccentric position of the nuclei, some of which took the stain very faintly or not at all. Here and there were noted areas of perivascular round cell infiltration. The vessels were congested throughout the gray and white matter. In the anterior horns were found several hemorrhagic areas. The extravasation seemed to follow the course of blood vessels in some places, although no break in the structure of the latter could be demonstrated (fig. 5). In preparations stained with sudan III, fat droplets were found in abundance in most of the nerve cells of the anterior horns (fig. 6). With cresyl-violet, the chromatolysis and morphologic changes in the neurons noted in the sections stained with hematoxylin and eosin were more definitely visualized. In Weil preparations myelin degeneration could not be demonstrated. With van Gieson's method there was no increase noted in the fibrous tissue of the meninges or cord. With Davenport's stain the increase in neuroglia and changes in the neurons already noted were again clearly demonstrated.

Although the changes described were definite they cannot be considered characteristic of this disease, since similar changes in the spinal cord may occur in toxic states other than those associated with psittacosis.

Bacteriologic Examination—Tissue from the lung, liver and spleen, secured under aseptic precautions, was submitted to Dr. G. P. Berry of the Rockefeller Institute for bacteriologic study. Dr. Berry reported that he identified and isolated the psittacosis virus from each of these tissues. He also isolated the virus from the sputum of one of the survivors (Mrs. B¹) and from the liver and spleen of the last remaining parrot received from the home of one of the survivors (S). (Without the work done by Dr. Berry a definite bacteriologic diagnosis of psittacosis could not have been established in this case.)

COMMENT

A considerable amount of literature has recently been published dealing with the various phases of this interesting disease. To avoid repetition, therefore, only the pertinent facts concerning this subject will be reviewed, omitting the clinical aspects which will be the subject of a subsequent publication by Dr. Meyer Rabinowitz.

In the epidemiologic report on psittacosis published by the League of Nations,¹ this disease is defined as one due to an unknown patho-

1 Roubakine, A. Monthly Epidemiological Report of League of Nations, no. 1, 1930 (an excellent review with full references).

genic agent, and transmitted to man by certain species of parrots and especially by parrots from the Amazon

The disease was first described by Jurgensen,² in 1876, as an atypical pneumonia of animal origin. The first recognized epidemic occurred in and around Paris and Switzerland in 1879, and was described by Wagner³ and by Ritter and Uster,⁴ respectively. All victims had been in contact with sick parrots from tropical countries. Since then epidemics have occurred in various parts of the world at frequent intervals. There was an epidemic in Bonn in 1882, in Leipzig in 1886, in Paris in 1892 and 1896, in Italy in 1894, in Berlin in 1898, in Brazil in 1904, in New Hampshire in 1904, in Zulprich (Rhineland) in 1909, in England in 1914, in Wilkes-Barre, Pa., in 1917, in Edinburgh in 1924, in Pennsylvania again in 1928 and in England again in 1929. Up to the end of 1929, there occurred, according to Heymann,⁵ a total of 164 cases, with 54 deaths. Between the end of 1929 and the beginning of 1930, however, much more severe epidemics occurred in the following locations: Argentina, Germany, England, Austria, Czechoslovakia, the Netherlands, Denmark, Switzerland, Poland, Spain, Portugal, Algeria and, last but not least, the United States of America. In this country outbreaks occurred in sixteen states, including the Hawaiian Islands. During these few months about 400 cases of psittacosis were reported throughout the world and more than one fourth of these occurred in the United States.

All the cases reported in this country were traced to one or two consignments of parrots from South America, so that on Jan. 4, 1930, the President was forced to prohibit the import of parrots into the United States. Since then, however, sporadic cases and epidemics have been reported in this country. McCoy⁶ reported the cases of several laboratory workers, from the Hygienic Laboratory of Washington, D. C., who were afflicted with the disease after exposure to infected parrots with which experiments were being carried out. Gorham, Calder and Vedder⁷ reported cases in New York State, Haines⁸ in Ohio, Bortz and Green⁹ in Pennsylvania, Wirth¹⁰ in New Orleans,

2 Jurgensen, in von Ziemssen. *Handbuch der allgemeinen Therapie*, Leipzig, F. C. W. Vogel, 1874.

3 Wagner. *Der sogenannt Pneumotype*, *Deutsches Arch. f. klin. Med.* **35** 191, 1884, **42** 405, 1888.

4 Ritter and Uster. *Deutsches Arch. f. klin. Med.* **25** 53, 1880.

5 Heymann, B. *Klin. Wchnschr.* **5** 193, 1930.

6 McCoy, G. W. *Pub. Health Rep.* **45** 843, 1930.

7 Gorham, L. W., Calder, F. G., and Vedder, J. D. *Psittacosis*, *J. A. M. A.* **94** 1816 (June 7) 1930.

8 Haines, H. G. *Psittacosis*, *J. A. M. A.* **94** 1821 (June 7) 1930.

9 Bortz, E. L., and Green, B. *Psittacosis*, *J. A. M. A.* **95** 400 (Aug. 9) 1930.

10 Wirth, W. R. *New Orleans M. & S. J.* **83** 132, 1930.

Rivers, Benjamin and Berry¹¹ in New York (another case resulting from contact with sick parrots in the laboratory during experimental investigations), MacLachlan, Permar and Rogers¹² in Pittsburgh, Peterson Spalding and Wildman¹³ in Washington, Wellman¹⁴ in Massachusetts, Sandoer and Coburn¹⁵ in Kansas, Hahn¹⁶ in Connecticut and Badger¹⁷ in a department store of a certain city in the United States, the name of which is not stated

The greatest number of cases have been caused by contact with the Brazilian green parrot known as the Amazon parrot. The disease, however, has been shown to be transmitted also by the gray parrot of Africa, love-birds, canaries, thrushes and the Italian cardinal bird. Psittacosis may also be contracted by domestic fowls, mice, bullfinches, rabbits and even cats.

Those familiar with the conditions of the trade in parrots are of the opinion that the poor conditions of transportation and the change in climate and general environment¹⁸ of these wild birds light up a latent psittacosis infection and make them ready hosts for the disease¹⁹. It is not known, however, how long a newly imported parrot may be a potential source of danger.

Direct contact with the infected animal is not the only way in which the disease may be contracted. Infection by fomites is a recognized possibility. This is supported by the case described by Horder and Gow²⁰. Human transmission of the disease is also possible, according to some investigators. Such cases have been reported by Hegler,²¹ Kerschenshteyner,²² Stefanopoli,²³ Cosman²⁴ and Sturdee and Scott²⁵.

11 Rivers, T. M., Benjamin, B., and Berry, G. P. Psittacosis, *J. A. M. A.* **95** 577 (Aug. 23) 1930.

12 MacLachlan, W. W. G., Permar, H. H., and Rogers, C. A. *Ann. Int. Med.* **4** 260, 1930.

13 Peterson, E., Spalding, O. B., and Wildman, O. Psittacosis, *J. A. M. A.* **95** 172 (July 19) 1930.

14 Wellman, H. E. *New England J. Med.* **203** 421, 1930.

15 Sandoer, S. A., and Coburn, C. E. *J. Kansas M. Soc.* **31** 28, 1930.

16 Hahn, T. F., Jr. *Yale J. Biol. & Med.* **2** 417, 1930.

17 Badger, L. F. *Pub. Health Rep.* **45** 1403, 1930.

18 Gordon, M. *Proc. Zool. Soc. Lond.*, 1928, pt. 2.

19 Parrots in Brazil in Relation to Psittacosis, Correspondence, *J. A. M. A.* **95** 876 (Sept. 20) 1930.

20 Horder, T., and Gow, A. E. *Lancet* **1** 442, 1930.

21 Hegler, C. *Deutsche med. Wchnschr.* **4** 148, 1930.

22 Kerschenshteyner. *Munchen med. Wchnschr.* **77** 310, 1930.

23 Stefanopoli. *Bull. san. de l'Algerie* **387** 54, 1930.

24 Cosman, quoted by Stefanopoli (footnote 23).

25 Sturdee, E. L., and Scott, W. M. A Disease of Parrots Communicable to Man (Psittacosis), Ministry of Health, Reports on Public Health and Medical Subjects, no. 61, London, His Majesty's Stationery Office, 1930 (another excellent review with an extensive bibliography).

There are several facts, however, that argue against psittacosis being a disease that may be spread from man to man. In the first place, the outbreaks do not assume real epidemic forms as do, for instance, those of influenza. They affect only household or family groups, in most cases contact with sick parrots can be proved. Secondly, the occurrence of epidemics coincides exactly with the import of a consignment of sick parrots and diminishes with the prohibition of their importation, ceasing entirely after all the sick parrots have died. Thirdly, it is difficult to ascertain beyond doubt that a given patient did or did not have contact with a sick parrot.

In reviewing the literature on the bacteriology of this disease one finds that numerous organisms have been associated with it. Thus, in 1888, Finkler²⁶ associated a streptococcus with this disease. In 1892 Netler and Gastou²⁷ demonstrated a pneumococcus in their cases. In 1893 Nocard²⁸ described the *Bacillus psittacosis* which he found in the marrow of parrots and in the wings of parakeets that died of this disease. This was later confirmed by Gilbert and Fournier,²⁹ who found the same organism in the heart's blood of one of his patients. In 1920, Peney³⁰ isolated from a parrot with psittacosis another similar organism, *Bacillus aettrycke*, which he considered to be the etiologic agent. In 1928, Thomson³¹ described as the cause of the disease another organism, similar to that described by Nocard. None of these, however, are today considered to be the cause of psittacosis because recently it seems to have been definitely shown that the malady is due to a filtrable virus. This was suggested by Bedson and his co-workers³² in 1930. Since then, European as well as American investigators have confirmed the theory and today the filtrable virus is accepted by most workers³³ to be the causative agent. It may also be added that Lillie³⁴ has reported finding certain minute, coccoid and bipolar, gram-negative, bacilliform inclusion bodies (*Rickettsia psittaci*) in the phagocytic cells of the alveolar exudate and in mononuclear cells of the alveolar walls.

26 Finkler, Z. *Kongr f inn Med*, 1888

27 Netler and Gastou, quoted by Sturdee and Scott (footnote 25)

28 Nocard, E. *Conseil d'hygiene du Departement de la Seine*, 1893

29 Gilbert and Fournier, quoted by Dubief. *Nouveau traite de medecine et de therapeutique*, Paris, 1920, no 1, p 306

30 Peney, H M. *Brit J Exper Path* **1** 131, 1920

31 Thomson, A P. *Practitioner* **124** 377, 1930

32 Bedson, S P, Western, G T, and Simpson, S L. *Lancet* **1** 235, 1930

33 Rivers, T M, Berry, G P, and Rhoads, C P. *Psittacosis*, *J A M A* **95** 579 (Aug 23) 1930. Krumwiede, C, McGrath, M, and Oldenbusch, C. *Science* **71** 262, 1931. Gordon, M H. *Lancet* **1** 1174, 1930. Armstrong, C, McCoy, G W, and Branham, S E. *Pub Health Rep* **45** 725, 1930

34 Lillie, R D. *Pub Health Rep* **45** 773, 1930

These bodies have been found to be associated with psittacosis, not only by the original observer but also by Levinthal,³⁵ Coles³⁶ and others

The clinical picture in psittacosis points to the involvement of two systems especially, namely, the respiratory and central nervous systems, represented by the pneumonia and the typhoid state respectively. Since the other organs show the usual changes found in general sepsis, only the most important observations concerning the pathologic changes in the lung and nervous system will be reviewed.

With regard to the pulmonary changes, there is some difference of opinion among pathologists. According to Oberndorfer,³⁷ the gross and microscopic observations in psittacosis are almost identical with those in influenzal bronchopneumonia. Confluent bronchopneumonia, bronchitis and bronchiolitis have been described by Hederschee³⁸ and

Points of Differentiation in the Pulmonary Pathology of Psittacosis and Influenza

Type of consolidation	Psittacosis		Influenza
	Lobar		
Cells lining the alveoli	Marked hyperplasia and hypertrophy		Nodular, even when areas of consolidation become confluent
Type of cellular exudate	Polymorphonuclear cells are absent or scarce, exudate consists of mononuclear, plasma and desquamated epithelial cells		No marked change Numerous polymorphonuclear cells, occasionally to the extent of suppuration
Relation of bronchi to areas of consolidation	None, bronchioles involved by extension of process from the surrounding lung tissue		Definite, capillary bronchitis with bronchopneumonia
Fibrin deposit	Very abundant throughout		Scarce, except near involved bronchioles
Character of hemorrhagic lesion	Associated with capillary thrombosis and severe necrosis of lung tissue		Not associated with either
Bacteria in the lung tissue	Scarce or absent except in areas of secondary infection		In large numbers throughout the lung

others as the basic change in the lungs in this disease. Contrary views, however, are held by most pathologists, including such authorities as Wilson³⁹ and Turnbull,⁴⁰ who found the changes to be, as Sturdee stated it, "different from anything they have previously seen."

Since so much controversy is centered about the resemblance between psittacosis and influenzal pneumonitis, it will perhaps be helpful, for purposes of emphasis, to tabulate the points of differences between these two conditions (see table)

³⁵ Levinthal, W. Klin. Wchnschr. **9** 654, 1930

³⁶ Coles, A. C. Lancet **1** 1011, 1930

³⁷ Oberndorfer. Munchen med. Wchnschr. **77** 311, 1930

³⁸ Hederschee. Nederl. tijdschr. v. geneesk. **8** 873, 1930

³⁹ Wilson, G. H. J. Path. & Bact. **33** 957, 1930

⁴⁰ Turnbull, quoted by Hutchison, R., Rowlands, R. A. and Levy-Simpson, S. Brit. M. J. **1** 633 (April 5) 1930

Other less constant changes which may be of aid in recognizing the pneumonitis of psittacosis are the dark, purplish-blue color of the lung, the relative absence of pleural exudate and the occurrence of small sub-pleural hemorrhages

The literature on the changes in the central nervous system in psittacosis is very scant, yet as was indicated, the clinical picture points to extensive involvement of this system, to wit, the photophobia, lethargy, stupor, sluggish speech, slow response, muttering delirium, incontinence, severe backaches, ataxia in convalescence and even localizing signs, such as facial immobility and muscle jerks. All these signs must be based on anatomic changes in either the brain or the spinal cord. Sturdee stated that congestion and edema in these organs are not infrequent findings. The references to studies on these organs, however, are very few. In one case studied by Oberndorfer, no changes were found in either the brain or the cord. Turnbull reported finding ring hemorrhages in the brain and cord in two of Hutchison's cases⁴¹. Hegler found multiple foci of softening in one case. Wilson found no brain lesions except atrophy of convolutions beneath a thickened and opaque pia-arachnoid. Hederschee found internal hemorrhagic pachymeningitis and a mixed coagulum in the sagittal sinus. Peterson found the following changes in one case in which he performed an autopsy. In the brain there was compression of the ventricles with marked dilatation of the veins along the septum and tela choroidea. The caudate nucleus contained large ring hemorrhages. The corpus callosum, internal capsule, putamen and thalamus were the seats of punctate hemorrhages. The hemorrhages showed a tendency to be elongated in the direction of the nerve fibers, with an occasional zone of necrosis in the center. There was also an infiltration with phagocytes and occasional lymphocytes and polymorphonuclear cells. Circumscribed areas of degeneration of myelin were also demonstrable. The spinal cord was not described.

These are the changes thus far uncovered in the nervous system for the neurologist to correlate with the clinical signs. How much these changes contribute to the cause of death is at present difficult to state. The vital centers of those dying with signs of marked central nervous system involvement may be sufficiently injured to be more than a mere contributory factor in the cause of death. In those who recover, however, there are apparently no residual neurologic changes, indicating that in these cases whatever injuries to the nerve tissue occurred were not permanent. It is obvious that in psittacosis the central nervous system needs much more careful study than it has been given heretofore.

⁴¹ Hutchison, R., Rowlands, R. A., and Levy-Simpson, S. *Brit. M. J.* **1**: 633, 1930.

CONCLUSION

The results of postmortem and bacteriologic examination in a case of psittacosis are reported. This case was one of a household epidemic in which five were afflicted with the disease, with two deaths, and which was traced to contact with newly imported parrots that were found to be suffering from psittacosis.

The pathologic changes found in the lung and spinal cord are especially emphasized. The resemblance between the pneumonia of psittacosis and influenza being a controversial subject, the points of difference between these two conditions are tabulated. In view of the fact that the clinical signs in this disease point to marked involvement of the central nervous system, the changes in the latter are described in detail. The scarcity of information in the literature on this phase of the subject is pointed out and a plea is made for more studies on the changes in the central nervous system in psittacosis.

The history, epidemiology and bacteriology of psittacosis are briefly reviewed.

THE EFFECT OF NITRITES ON PAIN AND ON THE MOTILITY OF THE GASTRO- INTESTINAL TRACT

I CLINICAL STUDY *

ARGYL J BEAMS, M D

CLEVELAND

That nitrites have some action on the gastro-intestinal tract was first called to my attention in July, 1926, when a patient, who was being treated in the hospital by the Sippy method for a duodenal ulcer, complained of precordial pain. The intern interpreted this pain as angina pectoris because he found a slight elevation of the blood pressure during these attacks. For this reason amyl nitrite was given to the patient to inhale. The pain was relieved promptly. During a subsequent attack of pain a duodenal tube was passed, and aspiration of the gastric contents, which were high in acidity, gave as prompt relief as the amyl nitrite. An increase in the dose of alkalis stopped the attacks.

This experience led me to investigate the effect of nitrites on the gastro-intestinal tract in other patients who were suffering with disease of the stomach and intestines.

METHOD

This study comprises two types of observations made on patients (1) observations to determine the effects of nitrites on abdominal pain of gastric or intestinal origin and (2) observations to determine the action of these drugs on the motility of the stomach and intestines.

Observations were made on 60 patients having abdominal pain arising from the stomach or intestines. 20 with duodenal ulcers, 10 with gastric ulcers, 3 with pyloric stenosis, 20 in whom the only apparent cause of the pain was hypermotility, pyloric spasm or hyperacidity, and 7 with intestinal cramps.

Amyl nitrite, nitroglycerin and sodium nitrite were the preparations used. Amyl nitrite was used in most instances because it acted more promptly, and the dose giving the desired physiologic action was more readily controlled than it was with the other preparations. The amyl nitrite was administered by having the patient inhale the fumes of one or two "pearls" crushed in a piece of gauze. They inhaled the fumes until they complained of such subjective symptoms as throbbing in the

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head, slight dizziness or a warm flush feeling, or until there were objective signs, such as a rapid pulse or a fall in blood pressure. This usually required from one-half to one minute's inhalation of the amyl nitrite.

Nitroglycerin was administered by placing the drops on the patient's tongue, beginning with 3 drops and increasing the dose by a drop every two minutes until symptoms showing a reaction to the nitrite appeared. The average dose required was about 7 or 8 drops.

The action of nitrites on the motility and tone of the stomach and intestines was studied by observing their effect on the gastro-intestinal tract during fluoroscopic examination. The same technic of administration was employed as has already been described. Observations were made on 200 persons, a group of normal individuals and on patients who showed hypermotility, spasm or some filling defect of the stomach or intestines.

In order to rule out the possible psychic action from the inhalation of amyl nitrite, observations were made on a group of patients after the inhalation of aromatic spirits of ammonia and amyl acetate. Ammonia was chosen because of the ease with which its penetrating odor produces reflex or psychic reactions. Amyl acetate was chosen because the odor is similar to that of amyl nitrite.

RESULTS

Amyl nitrite gave complete relief from pain in twelve of the patients with duodenal ulcer, partial relief in four and no relief in four. The pain was relieved for from five to twenty minutes. No explanation can be offered for the difference in the manner in which the patients responded to the amyl nitrite as all of them had simple duodenal ulcer without complications.

Six patients with gastric ulcer obtained relief of pain for from five to fifteen minutes after inhalation of amyl nitrite, whereas in four patients with penetrating gastric ulcer the pain was not controlled.

In three patients with pyloric stenosis proved by operation in whom visible peristalsis was observed, amyl nitrite not only relieved the pain but caused cessation of the peristalsis. The peristalsis disappeared more promptly than the pain but reappeared in from three to five minutes while the pain was relieved for from five to ten minutes.

In the patients showing only spasm or hypermotility to explain the gastric pain, amyl nitrite gave complete relief from pain for from fifteen minutes to two hours, and in seven patients with intestinal cramps the pain was relieved for from ten to twenty minutes.

The action of glyceryl trinitrate on the gastro-intestinal tract was observed in a small number of patients on whom the amyl nitrite studies

were made. The only difference in the action of these two drugs was that amyl nitrite acted more promptly, and the duration of relief from pain was shorter.

Sodium nitrite was given to eight patients with duodenal ulcer for a period of one week. The dose was 1 grain (0.065 Gm.) three times a day. None of these patients had relief from pain, although they responded to amyl nitrite and glyceryl trinitrate. Two patients having duodenal ulcer with pylorospasm who continued to have pain on alkaline therapy and diet, obtained relief with the administration of sodium nitrite, and had a return of pain when sodium nitrite was discontinued. In twelve patients with gastric pain in whom spasm and hypermotility were the only findings, eight obtained relief from pain with sodium nitrite, and four obtained no relief.

In the group of patients on whom fluoroscopic studies were done, the most constant action of nitrites on the gastro-intestinal tract was cessation of peristalsis and diminished tone (figure). Of two hundred persons on whom fluoroscopic observations were made, only ten failed to show some response to nitrites. Five of these had duodenal ulcer and five showed no organic lesion. The duration of action was from two to five minutes with amyl nitrite, and from five to ten minutes with nitroglycerin.

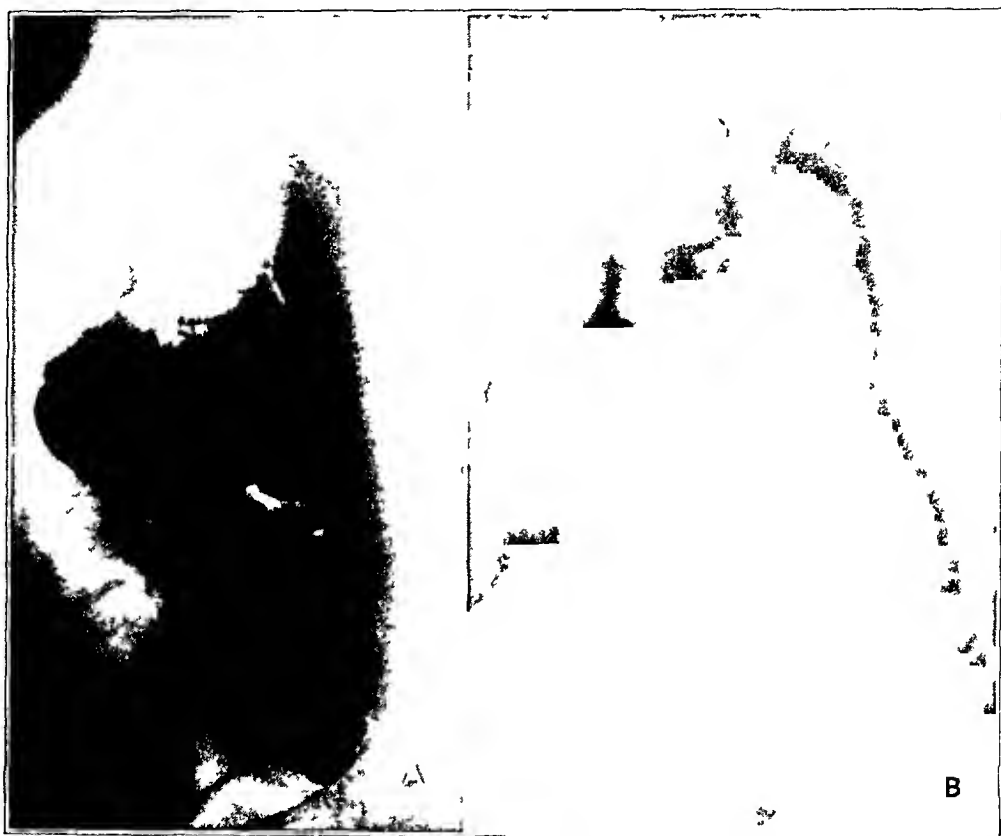
Deformities in the stomach or the intestines, the result of organic lesions, were unaffected, in fact, the deformity was accentuated when the uninvolved portion of the stomach or intestines relaxed. In several patients there were deformities of the gastro-intestinal tract which were not recognized until after amyl nitrite was administered. This was very well illustrated in a patient, 45 years of age, with a history of weakness, loss of weight and some distress after eating of three months' duration. The physical examination gave negative results, and the fluoroscopic examination revealed a slight unevenness in the upper third of the stomach, which was thought to be of no importance. After the administration of amyl nitrite, the peristalsis ceased and the stomach was more relaxed, except for this region which appeared then to be a definite deformity. Operation revealed carcinoma.

Only six patients were observed to have abdominal pain during fluoroscopic examination. In all these patients vigorous peristalsis was seen during the paroxysms of pain. Administration of amyl nitrite stopped the peristalsis and the pain simultaneously. Repeated trials were made during the course of the examination, with the same result.

Pylorospasm did not yield to nitrites as readily as might be expected. Only eight of seventeen patients who were observed with pylorospasm, showed relaxation when nitrites were administered. Six of these cases were extrinsic in origin, and two were presumably intrinsic, for there were deformities of the duodenal cap typical of duodenal ulcer.

Of the nine cases that were not modified by the nitrites, seven were extrinsic and two intrinsic in origin. Only three cases of cardio-spasm were observed in this study, two of them showed complete relaxation, and one was not modified by the nitrite.

All the patients showing no relaxation of the pylorus or cardia in response to nitrites were subsequently observed after the administration of atropine, and it was found that atropine was no more effectual than the nitrites.



Roentgenograms showing the effect of amyl nitrite on the tone and peristalsis of the stomach. *A*, stomach showing active peristalsis. *B*, after the inhalation of amyl nitrite for one-half minute, peristalsis ceased and tone diminished.

There were twelve patients in whom fluoroscopic examination of the colon showed obstruction to the passage of barium or marked spasticity that was suggestive of an organic lesion. However, amyl nitrite caused complete filling and free passage of barium, while colons with proved organic lesions were not modified.

A number of patients showing a definite response to nitrites were given aromatic spirit of ammonia or amyl acetate to inhale. None of these patients had any relief from pain, and there was no modification of the peristalsis. This apparently ruled out the possibility of a psychic reaction to the inhalation of amyl nitrite.

REVIEW OF THE LITERATURE AND COMMENT

Up to the present time few observations on the effect of nitrites on the gastro-intestinal tract have been recorded. The relief from abdominal pain obtained by the administration of nitrites was first reported by Frank¹ in 1875. He found that intestinal cramps caused by lead poisoning were relieved by amyl nitrite. Pal² confirmed this action of amyl nitrite, and also showed that gastric crises and angina abdominalis were relieved by amyl nitrite. In 1915 Hirschfelder³ found that vigorous peristalsis and spasm of the intestines produced by lead poisoning in animals were inhibited by amyl nitrite. In fluoroscopic studies of patients Holmes and Dresser⁴ found that amyl nitrite caused cessation of peristalsis and was equal to atropine as an antispasmodic. In the present study there has been found a definite action of nitrites on certain types of abdominal pain, and a very constant action on the motility of the stomach.

The cessation of peristalsis and the diminution in the tone of the stomach and intestines appear to be the only mechanism of the action of nitrites responsible for the relief from pain. Proofs for this action are (1) cessation of peristalsis or diminution in tone in 95 per cent of all cases studied, (2) complete relief from pain observed in all patients in whom alteration of motility or tone were the only apparent causes of pain, (3) the cessation of peristalsis with diminution of tone and relief from pain simultaneously, observed during the fluoroscopic examination of some of the patients, (4) disappearance of visible peristalsis and pain in patients with pyloric stenosis when nitrites were administered, (5) no effect on the secretory function of the stomach.

In the group of patients with organic lesions, there were twelve who obtained no relief from pain but showed a cessation of peristalsis and diminished tone when nitrites were administered. The difference in the response to nitrite suggests two possibilities. 1. There may be some other cause for the pain than gastric tonicity or motility, since it has been found that whenever motility or tone is the cause of pain, nitrites give relief. 2. The tone of the muscle about the ulcer cannot be modified by nitrites when the lesion involves the muscular coats by direct extension or edema. The latter view is supported to some extent by the manner in

1 Frank, August. Ueber die Veränderungen am Circulationsapparate bei Bleikolik, *Deutsches Arch f klin Med* **16** 423, 1875.

2 Pal, J. Die vasomotorischen Begleiterscheinungen der lanzinierenden Schmerzen und das Alternieren der tabischer Krisen, *Wien med Wchnschr* **54** 1, 1904.

3 Hirschfelder, Arthur D. Pathologic Physiology of Lead Colic. Its Relation to Experimental Therapeutics, *J A M A* **65** 516 (Aug 7) 1915.

4 Holmes, G W, and Dresser, Richard. The Use of Amyl Nitrite as an Anti-Spasmodic, *Am J Roentgenol* **19** 43 (Jan) 1928.

which the patients with gastric ulcers responded. The only patients of this group who failed to obtain relief from pain were those with penetrating ulcers. This does not offer an explanation for the failure of response in the other patients, but it suggests the possibility that when an ulcer involves the muscular coats it may not be modified by nitrites.

The action of nitrites on the pain of gastric and duodenal ulcers supports the theory that the pain is dependent on the motility and tone of the stomach rather than directly on the acidity. There is no doubt, however, that the acidity is an important factor in the cause of pain, as has been pointed out by Gonniger,⁵ Palmer⁶ and others. It is quite possible that in some manner the acidity may control the tone of the stomach.

One other important fact called to attention by this study is the unreliability of using nitrites as a diagnostic means to differentiate angina pectoris from certain upper abdominal conditions that may give rise to precordial or substernal pain, and in those cases of upper abdominal pain in which the question of angina pectoris arises.

The most constant effects of nitrites observed in the fluoroscopic studies were the cessation of peristalsis and the diminution of tone in the stomach and intestines. This action has been a great aid in differentiating deformities of functional origin from those of organic origin. This was especially true in the fluoroscopic examinations made on the colon. The functional spasm of the colon were relaxed, whereas the organic deformities were unmodified.

CONCLUSIONS AND SUMMARY

1 The effect of nitrites on abdominal pain arising from the gastrointestinal tract was observed in sixty patients. All of the patients without organic lesions were relieved by the nitrites, whereas of thirty-three with organic lesions only twenty-one were relieved.

2 Evidence has been offered which indicates that the relief from pain by the nitrites is dependent on the cessation of peristalsis and the diminution in tone. The failure to obtain relief is probably due to the inability of the muscle to relax.

3 Of 200 patients observed in the fluoroscopic studies only 10 failed to show cessation of peristalsis and diminution of tone in the stomach and intestines following the use of nitrites.

4 Nitrites have been found to be a great aid in differentiating organic deformities from functional ones.

5 As an antispasmodic nitrites are to be preferred to atropine, but neither is wholly satisfactory.

⁵ Gonniger, M. Zur Diagnose des Ulcus ventriculi, Berl klin Wchnschr **45** 396, 1908.

⁶ Palmer, W. L. Mechanism of Pain in Gastric and Duodenal Ulcer, Arch Int Med **39** 109 (Jan.) 1927.

THE EFFECT OF NITRITES ON THE MOTILITY OF THE GASTRO-INTESTINAL TRACT

II EXPERIMENTAL STUDY *

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Amyl nitrite has been used extensively in the treatment for angina pectoris and hypertension since its introduction by Lauder Brunton in 1867. Numerous observations, both clinical and experimental, have been made on the action of nitrites on the circulatory system, but very little attention has been directed toward other possible actions of these compounds. The only clinical observations made on the action of the nitrites on the gastro-intestinal tract are those of Reigel and Frank, Pal, and Holmes and Dresser, already referred to in a previous paper¹. The only experimental work is that of Hirschfelder, who found that nitrites caused cessation of peristalsis in rabbits and cats suffering from experimental lead colic, and who also showed that this action was not vascular in origin but probably a direct action on the intestines.

In a clinical study of the effect of nitrites on the gastro-intestinal tract, it has been found that certain types of abdominal pain were relieved and that the motility of the stomach and intestines was modified by nitrites. The mechanism of this action was not determined from these studies, but several possibilities were suggested: (1) reflex action, (2) vascular action and (3) direct action on the intestines.

The present study was undertaken with the hope of determining the mechanism of this action on the gastro-intestinal tract.

METHODS

Three groups of animal experiments compose this study: (1) fluoroscopic studies of the gastro-intestinal tract, (2) direct observations on the stomach and intestines and (3) observations on the isolated stomach and on intestinal segments.

1. Fluoroscopic studies were made on the gastro-intestinal tracts of dogs and cats. Some of the animals were not anesthetized, while in others barbitol sodium (225 mg per kilogram of body weight) was employed intraperitoneally or intravenously as the anesthetic. An amount of barium sulphate sufficient to fill the

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1. Beams, A. J. The Effect of Nitrites on Pain and Motility of the Gastro-Intestinal Tract. I. Clinical Study, Arch. Int. Med., this issue, p. 270

stomach moderately was given by tube. Nitrites (amyl nitrite, glyceryl trinitrate and sodium nitrite), amyl acetate and pilocarpine were administered during the course of the fluoroscopic examination. The amyl nitrite and amyl acetate were given by placing 8 or 10 drops of the drug on a piece of gauze and holding it over the animal's nose and mouth. Spirits of glyceryl trinitrate (0.05 cc per kilogram) and sodium nitrite (20 mg per kilogram) were given intravenously.

The action of the nitrites on the gastro-intestinal tract was also observed after the administration of pilocarpine (1.5 cc of 2 per cent solution intravenously or subcutaneously).

2 In the second group of experiments, direct observations were made on the stomach and intestines during the administration of nitrites, amyl acetate and pilocarpine. The animals employed in these studies were dogs, cats and rabbits. There were ten animals studied, on which over forty observations were made.

Under barbital anesthesia (intraperitoneal administration) the femoral vein was cannulated, a tracheal cannula inserted, and the abdomen opened in the midline. Sutures were passed through the edges of the abdominal wall and fastened to rods on either side for the purpose of making an extensive exposure of the gastro-intestinal tract. The stomach and intestines were covered with liquid petrolatum.

A careful study was made of the motility of the stomach and intestines, the frequency of the peristaltic waves and the degree of tone before and after the administration of nitrites, amyl acetate and pilocarpine being especially observed. The same technic was followed in the administration of the drug as was described previously, except that amyl acetate and amyl nitrite were inhaled through the tracheal cannula, the possibility of reflex nasopharyngeal irritation thus being eliminated.

3 Kymographic tracings of the rhythmic contractions of isolated intestinal segments of rabbits and of the stomachs of rats were made. The intestinal segments (about 3 cm in length) were attached to an apparatus for recording the longitudinal contractions, and then placed in a 50 cc warming chamber containing either a normal Locke's solution or Locke's solution the p_{H} of which was corrected with sodium hydroxide rather than with sodium bicarbonate. During the early part of these experiments the latter solution was used accidentally, and it was observed that sodium nitrite acted differently than with the normal Locke's solution. For this reason it was employed in all of the experiments. The solutions were aerated and maintained at a temperature of 38 C.

Tracings of the rhythmic contractions of the intestinal segments were recorded on smoked drums before and after the addition of amyl nitrite, sodium nitrite, amyl acetate or sodium chloride in dilutions of from 1:50 to 1:100,000.

RESULTS

Fluoroscopic Studies—Cessation of peristalsis and relaxation of the stomach was always observed subsequent to the administration of nitrites, with the exception of amyl nitrite, which infrequently failed to have any effect on the motility. The action of all the nitrites appeared about one-half minute after the administration. With amyl nitrite the effect lasted from three to five minutes, with glyceryl trinitrate from five to ten minutes, and after sodium nitrite from ten to twenty minutes. Amyl acetate had no effect on the motility or tone. This confirms the action already noted in man. The administration of

pilocarpine (subcutaneously) caused vigorous peristalsis in the stomach and intestines. This action occurred in from about two to three minutes after the drug had been given. Nitrites were quite as effective after as before the administration of pilocarpine, although the effects noted were of shorter duration.

Direct Observations on the Stomach and Intestines—In the experiments in which direct observations were made on the motility of the stomach and intestines, an excellent opportunity was offered to study the action of nitrites more in detail and to obtain fairly accurate measurements of the duration of the action. Amyl nitrite was the only nitrite preparation that failed to produce some response every time it was administered. In one animal amyl nitrite was ineffective, in two others it was ineffective on first administration, although subsequently a definite response was obtained.

About one-half minute after the administration of amyl nitrite, the peristaltic waves of the stomach became shallow and were less frequent, and some of them faded out before reaching the pylorus. At the end of one minute, the waves were entirely absent, and there was relaxation of the stomach. The duration of amyl nitrite was from two to five minutes. In most of the experiments the small and large intestines acted in the same manner as that described for the stomach. In a few instances no action was seen in the intestine, although the stomach responded. The duration of action was the same in both. Inhalation of amyl acetate had no effect on the peristalsis. Glyceryl trinitrate and sodium nitrite had the same effect as that described with amyl nitrite, except that the duration of action was longer and there appeared to be a more definite response. The duration of the action of glyceryl trinitrate was from three to ten minutes, and that of sodium nitrite from five to twenty minutes.

After the administration of pilocarpine, vigorous peristaltic waves were seen in the stomach and intestines. The waves were very deep, and from six to eight contractions per minute were observed in the stomach. The nitrites continued to have the same inhibitive effect on the motility of the stomach and intestines as they had before the administration of pilocarpine. The duration of the action was shorter, and at times, with the administration of amyl nitrite, the only change noted was a slowing and very shallow peristaltic waves that failed to reach the pylorus. However, with glyceryl trinitrate and sodium nitrite the action was striking. One minute after the administration of the glyceryl trinitrate or sodium nitrite the vigorous peristalsis and hypertonicity of the gastro-intestinal tract were replaced by relaxation and inactivity.

Observations on the Isolated Stomach and Intestines—With amyl nitrite a very constant effect was seen in all of the experiments. Immediately following the introduction of the drug into the chamber of Locke's

solution there was a sudden diminution in the tone and cessation of the rhythmic contractions (fig 1) This lasted from one to three minutes Then there was a gradual improvement in the tone, amplitude and frequency with complete recovery at the end of from four to ten minutes There appeared to be a definite relation between the duration of the action and the amount of drug introduced

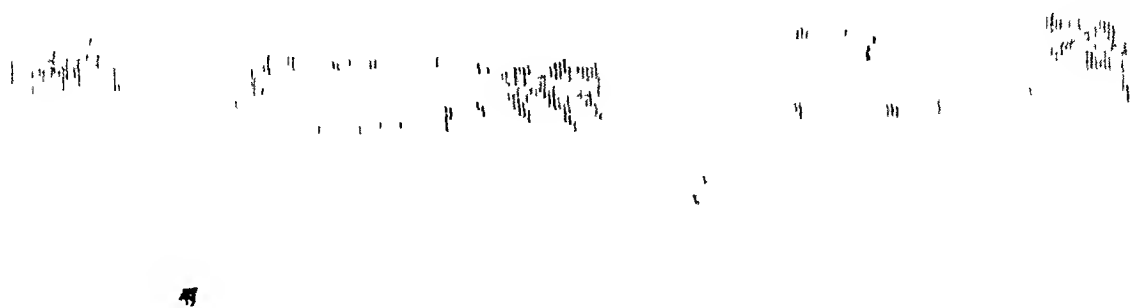


Fig 1—Tracing of an intestinal segment showing the effect of amyl nitrite Immediately following the introduction of the drug, there was a fall in tone and a cessation of rhythmic contractions

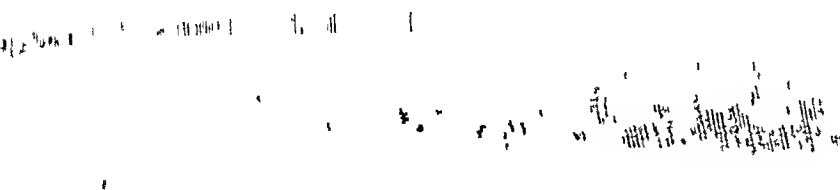


Fig 2—Tracing of an intestinal segment immersed in Locke's solution No change was seen in the rhythmic contractions until after a total of 0.5 cc of a 10 per cent solution of sodium nitrite had been introduced The contractions were then irregular, with a decrease in amplitude until they ceased entirely

Sodium nitrite did not cause as constant or prompt an action as amyl nitrite In the experiments in which the normal Locke's solution was employed, the effect most frequently observed was a gradual decrease in the amplitude and frequency of the contraction over a period of ten or fifteen minutes, when contractions entirely ceased (fig 2) Recovery was uncommon

The action of sodium nitrite was more constant in the Locke's solution p_H corrected by sodium hydroxide than in normal Locke's solution. Immediately following the introduction of sodium nitrite there was a definite increase in tone with a marked diminution in amplitude and frequency of contractions (fig 3). The rise in tone was of short duration (lasting from one-half to one minute), and was followed by a gradual fall, so that the terminal level was far below its original level. With the fall in tone, a temporary improvement in the amplitude and frequency occurred, but as the tone decreased, the amplitude and frequency became less until often the contractions entirely disappeared. In many cases recovery did not occur, but as a rule recovery was observed. In those

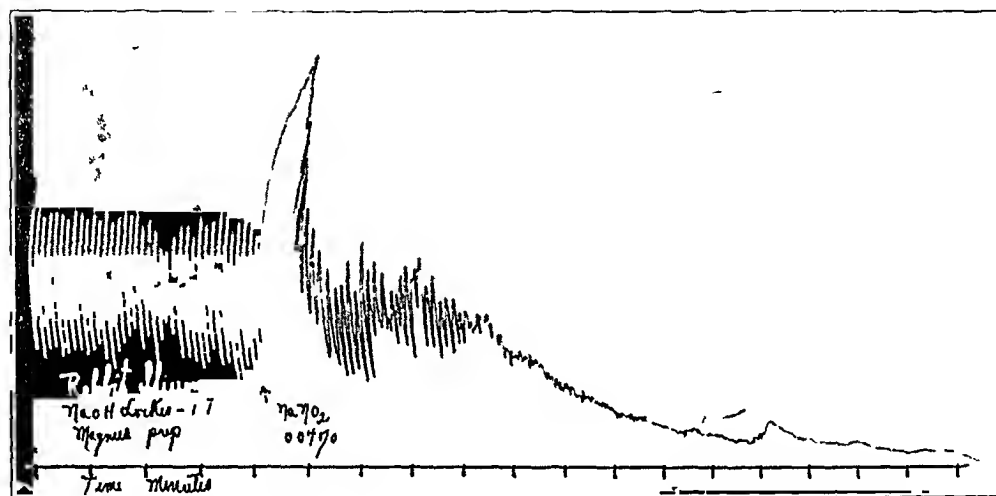


Fig 3—Tracing of an intestinal segment immersed in Locke's solution, the p_H of which was corrected by sodium hydroxide. The arrow indicates the introduction of 0.2 cc of a 10 per cent solution of sodium nitrite (0.04 per cent). There was first a rise and then a fall in the tone, with a gradual diminution in the amplitude of the contractions.

segments in which partial recovery occurred, the contractions were arrhythmic, the rate was diminished and the contractions irregular. The tone usually remained below the original level.

Exceptionally, segments immersed in normal Locke's solution reacted in a manner quite similar to that of segments immersed in Locke's solution corrected by sodium hydroxide. As a rule, failure to respond to sodium nitrite was more frequent in the presence of normal (buffered) Locke's solution than in the Locke's solution of the same p_H corrected by sodium hydroxide.

Amyl acetate or sodium chloride had no effect on the intestinal segments even in much greater concentrations than that employed in amyl nitrite or sodium nitrite.

COMMENT

The fluoroscopic examinations and the direct observations made on the gastro-intestinal tracts of the animals studied offered very little information as to the mechanism of the action of nitrites

In the studies made on the intestinal segments, the nitrites caused a definite change in the rhythmic contractions and tone. This action of nitrites rules out the possibility of a reflex or vascular action, and places the site of action in the intestines. It is impossible to state whether or not it acts entirely on the muscle with the evidence that is offered.

The failure of amyl acetate to produce any effect on the intestinal segments rules out the amyl ion as a possible cause of the actions of amyl nitrite observed. Sodium chloride had no effect on the rhythmic contractions. It is quite probable therefore that neither the sodium ion or alterations of isotonic conditions are of significance in explaining the sodium nitrite reaction. The initial rise seen after the introduction of sodium nitrite in the Locke's solution with the p_H corrected by sodium hydroxide is not due to hypertonicity of the nitrite dosage that was added to the bath. No explanation of this reaction is offered, nor is there an explanation for the number of failures in the response in normal Locke's solution compared with Locke's solution buffered by sodium hydroxide.

TRANSIENT VENTRICULAR FIBRILLATION

A STUDY OF THE ELECTROCARDIOGRAMS OBTAINED FROM A
PATIENT WITH AURICULOVENTRICULAR DISSOCIATION
AND RECURRENT SYNCOPAL ATTACKS *

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It is now definitely established from recorded observations that transient syncopal attacks occurring in patients with permanent auriculoventricular dissociation are due in the main to one of two conditions, either to complete standstill of the ventricles or to the various grades of acceleration leading to ventricular fibrillation. The former mechanism, which is the more common, has been excellently reproduced in the dog, in which heart block had been established,¹ and from correlations with the clinical and graphic manifestations observed in man there is now a fairly accurate knowledge of some of the successive events leading to and following transient ventricular standstill.

Comparable analyses of the disturbances leading to the onset and recovery from transient ventricular fibrillation in the presence of auriculoventricular dissociation are lacking, for spontaneous recovery from ventricular fibrillation in the larger intact animal is unknown if the rhythm is induced by any of the methods now available.² Consequently, for the present at least, knowledge of the mechanism responsible for syncopal attacks in which ventricular acceleration instead of ventricular standstill takes place will have to come from careful observations on human beings subject to such seizures.

I am reporting observations on a patient who suffered sixty-seven seizures of unconsciousness during a period of seven months while she was at the Montefiore Hospital. The duration of these syncopal attacks varied from a little over one minute to the longest recorded seizure which lasted six minutes and two seconds and was followed by recovery. Electrocardiograms were obtained of all or of part of twelve such

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1 Erlanger, J. On the Physiology of Heart Block in Mammals with Special Reference to the Causation of Stokes-Adams Disease. Part II. On the Physiology of Heart Block in the Dog, *J. Exper. Med.* 8:8, 1906.

2 Wiggers, C. J. Studies of Ventricular Fibrillation Caused by Electric Shock. I. The Revival of the Heart from Ventricular Fibrillation by Successive Use of Potassium and Calcium Salts, *Am. J. Physiol.* 92:223, 1930.

seizures accompanied by syncope, and in each instance the underlying mechanism proved to be ventricular fibrillation

From numerous other electrocardiograms taken of this patient preceding, during and subsequent to her syncopal attacks, it has been possible to draw a fairly accurate picture of the successive alterations that took place in her heart rate and rhythm preceding and succeeding ventricular fibrillation

REPORT OF A CASE

History—G. S., a woman, aged 66 and weighing 112 pounds (50.8 Kg.), was admitted to the Montefiore Hospital on July 16, 1929, and died on Feb. 5, 1930. Her chief complaints on admission were progressive shortness of breath, weakness and recurrent attacks of loss of consciousness. Her symptoms were of one year's duration.

In January, 1928, the patient was informed for the first time that she had high blood pressure. She had been in good health up to that time. One day in February she suddenly dropped to the floor and became unconscious. It was observed by members of her family that during such seizures of unconsciousness, she showed twitchings of the face and upper extremities, with rolling of her eyes and profound stertorous breathing. Between February, 1928, and April, 1929, she experienced eight such seizures. Between these attacks she felt perfectly well, except for slight headaches, which were more pronounced in the morning. Since the middle of April, 1929, the attacks of unconsciousness had become more frequent, numbering at times several in one day.

In addition to these major and severer attacks, she also complained of briefer periods of giddiness and fainting sensations sometimes lasting only a few seconds and frequently accompanied by a consciousness of "palpitation" of the heart. She had had over thirty such spells during one day almost five weeks prior to her admission to the Montefiore Hospital, but since that time she had not had any major attacks of unconsciousness.

Examination—Examination on admission to the Montefiore Hospital revealed an elderly Jewish woman, slightly dyspneic, mentally clear and quite intelligent. Her lips were cyanotic, but her face and skin had a lemon yellow tint. All of her teeth were missing, which probably accounted for the fact that her tongue showed no signs of having been bitten during any of the periods of unconsciousness. Her pupils were equal, and both reacted to light and in accommodation. The right carotid artery was thickened, and near the lateral border of the sternomastoid muscle it was very stiff and tortuous. The superficial jugular veins were markedly distended, and 2 and sometimes 3 auricular beats could be seen pulsating to each ventricular contraction of the heart. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. The heart sounds were of poor quality, the first sound at the apex being very weak. Occasionally it would be loud, and at such times it was noted that the ventricular contraction occurred simultaneously with that of the auricle. The aortic second sound was markedly accentuated.

The pulses were slow, slightly irregular but of good force. The ventricular rate was approximately 38 beats per minute when counted over a period of several minutes. In the interventricular silences, 2 and sometimes 3 auricular sounds could be heard distinctly near the third intercostal space to the left of the sternum. The radial arteries were thickened and in parts beaded. The blood pressure was 280 mm. of mercury systolic and 80 mm. diastolic when the ventricular rate averaged 38 beats per minute.

Over the lungs posteriorly only a few moist râles could be heard. The abdomen was soft and lax, and the edge of the liver was palpable 6 cm. below the costal margin in the midclavicular line.

Roentgen examination of the chest did not reveal any abnormalities in the lungs. On fluoroscopic examination the pulsations of the left auricle could be seen independent of the ventricular contractions at the rate of about three and four auricular contractions to one ventricular contraction. The left ventricle was concentrically enlarged and had a high take-off. The aorta was wide and elongated and showed in its arch several calcific plaques.

An electrocardiogram taken on the day of admission revealed left ventricular predominance and complete auriculoventricular dissociation. The ventricular complexes were all of the supraventricular form. The basic ventricular rate varied from 177 beats per minute to 241 beats, and the auricular rate was 100 beats per minute. The T waves were markedly negative in all three leads. At times there was definite bigeminal rhythm, owing to premature ventricular beats.

Course—Although the patient had been free from symptoms for the preceding five weeks, one day after her admission to the Montefiore Hospital she began to complain of short recurrent spells of dizziness. At 4 30 p. m. on July 17, 1929, she was seen at the hospital in her first major syncopal seizure.

Preceding this attack she was standing, and her heart rhythm was found to be irregular, there being at times definite bigeminal rhythm. The basic ventricular rate averaged 40 beats per minute, not including the premature ventricular contractions. Infrequently, I could feel the pulse suddenly collapse for a few seconds, so that no beats were palpable at the wrist. During these short periods the patient's face would become pale, she would shut her eyes, shake her head a bit with a few twists of the shoulders and then open her eyes again and sigh very deeply when it was over. After a few such minor seizures, the patient became suddenly motionless and dropped into an arm chair. Her eyes became fixed, her face assumed an expressionless attitude and became almost deathly pale, and there was intense cyanosis of the lips. She suddenly stretched out her hands and legs stiffly, and her head turned involuntarily toward the left side and toward the back. Her eyes began to roll slowly and irregularly to the left and upward. She began to breathe stertorously with her mouth at first open and then shut tightly, using all of her accessory inspiratory muscles. She foamed at the mouth. A sudden convulsive seizure was followed by an intense flush of the face and neck which coincided with a barely perceptible slow pulse of about 45 beats per minute at first. This lasted only a few seconds, and was followed by a rapid pulse rate of about 100 beats per minute. The pulse rate slowed within four seconds to almost 40 beats again. With the onset of the rapid pulse rate, irregular auricular pulsations were again visible in the neck veins. As the patient regained her normal color she began to breathe more freely, and she asked for a drink of water.

This whole period of syncope lasted about two minutes, during which time no auricular pulsations were visible in the neck veins, nor was there any palpable pulse at the wrist.

The patient was seen again in another syncopal attack on July 22, at 12 10 p. m. At this time the pulse rate seven minutes prior to the seizure was 40 beats per minute and irregular. The auricular rate as counted from the pulsations of the veins in the neck was about 95 beats per minute. During this attack, which lasted exactly one minute and twenty seconds, clinical observations were carried out with only one point in view, and that was to study the auricular rate and rhythm, which was made possible by the markedly distended deep veins of the neck. Her pulse rate was counted at the same time.

During this seizure no auricular pulsations were visible, nor was there any palpable pulse at the wrist, and the heart sounds were totally absent. At the end of this attack, which was somewhat similar to the preceding one, faintly visible but rather frequent and irregular beats were seen in the neck veins. At first these averaged one to each beat felt at the pulse, then they increased in frequency to about 60 beats per minute within the next thirty seconds, and subsequently to 120 beats to the minute for the ensuing 50 seconds. The pulse rate was almost equal to the auricular rate, although it was slightly irregular and variable. Within two minutes after the cessation of the attack, there was definite coupling at the wrist, with the rate at 62 beats per minute. In another minute the pulse rate slowed to 44 beats per minute, and the auricular rate, which was now regular, averaged 100 beats.

Within the next five weeks of the patient's stay in the hospital, she was ambulatory and free from all symptoms. During this period she received 30 minims (1.84 cc) of saturated solution of potassium iodide daily. At first the frequency of the attacks in the ensuing weeks was attributed to the effects of the drug, but the seizures became even more frequent when the drug was omitted.

A total of sixty-seven syncopal attacks with epileptiform seizures were noted between the day of her admission to the hospital and the day of her death, when she was seen in her last attack, which lasted almost thirteen minutes but consisted of several rapid recurrent seizures of transient ventricular fibrillation, one following the other in rapid succession, with alternate restoration of the basic and dominant ventricular rate and rhythm.

ALTERATIONS IN THE ELECTROCARDIOGRAM PRECEDING VENTRICULAR FIBRILLATION

Prolonged observations on the patient whose case has been reported, following the first recorded attack and its premonitory period, have amply demonstrated the possibility of recognizing in her clinically the onset and appearance of transient ventricular fibrillation in practically the order revealed by the electrocardiograms.

Although the records of the several syncopal attacks differed slightly at both the onset and offset, depending in part on the duration of the seizures, the stages preceding the onsets of ventricular fibrillation were fairly constant and uniform, judging from the electrocardiograms obtained. It is probable that similar seizures in other patients with complete auriculoventricular dissociation and transient ventricular fibrillation are preceded by like events, differing only in the premonitory period, which may last, as in this patient, only a few hours at one time and several days at another.

The average basic ventricular rate oscillated between 28 and 36.5 beats per minute (fig 1). The lowest regular ventricular rate recorded was 17.5 beats per minute at a time when the patient was up and about. The Q-R-S complexes were all of the supraventricular form, but were followed by an unusually large, wide and completely inverted T wave. Infrequently, the Q-R-S complexes were variable from beat to beat.

in height as well as in duration, often assuming transitional changes from a dextrocardiogram to a levocardiogram and vice versa

In the intervals between the syncopal attacks, the basic ventricular rate was regular, and was not influenced by exercise or by sleep during the day. It was not affected by the subcutaneous administration of atropine sulphate in doses of $1/50$ of a grain (0.0019 Gm) or by pressure over either carotid artery or on the eyeballs.

A ventricular rate of 36 beats per minute could be increased temporarily, but only for a few minutes, to 41 beats, at a time when no

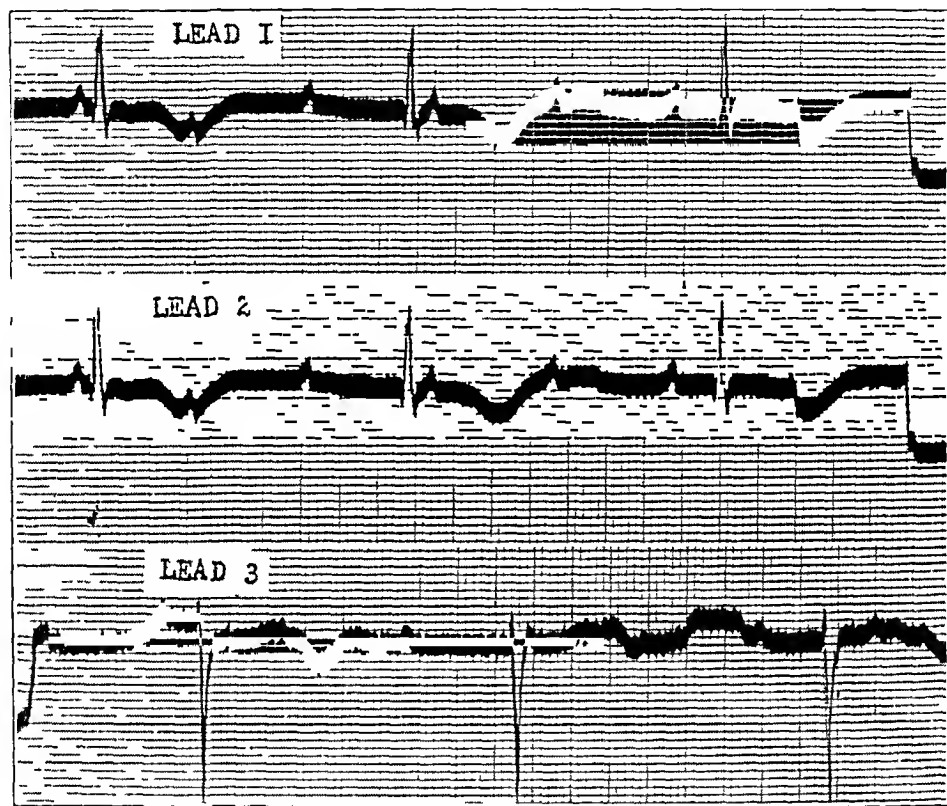


Fig 1—Left ventricular preponderance. Complete auriculoventricular dissociation. The ventricular complexes were all of the supraventricular form. The T waves were negative in all three leads. The basic auricular rate was 93.7. The basic ventricular rate was 36.5.

extrasystoles were present, by the subcutaneous injection of 0.5 cc of a 1:1,000 solution of epinephrine. No premature beats of the ventricles could be elicited in this way.

During the presence of a regular ventricular rate, the auricles also beat regularly, but their rhythm was independent of that of the ventricles. At times a slight irregularity was present because of shortening of the interauricular periods during the presence of a ventricular contraction. The auricular rate was easily accelerated temporarily by exercise and the subcutaneous administration of atropine sulphate in

doses of 1/100 grain (0.006 Gm.) subcutaneously. However, repeated pressure over the right carotid artery did not influence their rate or rhythm.

On several occasions when tracings and heart counts were made on the patient repeatedly throughout the day, the basic ventricular rate preceding the onset of ventricular fibrillation behaved somewhat similarly to that observed by me previously in a patient with complete auriculoventricular dissociation who had been deeply under the influence of toxic doses of digitalis.³

At first there was a gradual increase in the basic ventricular rate from an average of 28 beats during the presence of auriculoventricular dissociation to a ventricular rate of 42.8 beats, with the appearance of a partial heart block and a regular auricular rate of 83.3 beats, two auricular contractions being followed by one ventricular systole (fig. 2). After a few hours of this rhythm, which remained uninfluenced by effective doses of atropine or by carotid sinus pressure, there was a spontaneous increase in the rate of the auricles to 103.4 beats and the reestablishment of complete auriculoventricular dissociation with a 5:2 sequence (fig. 3 A-E).

Clinically, this rhythm resembled somewhat that of a bigeminy, but the electrocardiograms revealed this irregularity to be due to an adaptation of certain auricular contractions to that of the ventricles, producing alternately prolonged and shortened interventricular periods depending on the simultaneous contractions of each third auricular beat to that of the ventricles.

In the electrocardiograms, the Q-R-S deflections appearing at the time of a superimposed contraction invariably assumed the form of a dextrocardiogram (fig. 3 A, C). This was not merely a fortuitous observation, since it was encountered on more than one occasion when records were taken over a long period of time.⁴

This condition, simulating a bigeminal rhythm clinically, after persisting for a little over one hour at one time and several hours at another was suddenly transformed into a 2:1 heart block, with an increase of the ventricular rate to 46.8 beats per minute and an auricular rate of 93.7 beats, whereas previously the auricles had a rate of 103.4 beats (fig. 3 E-F).

A further increase in the dominant ventricular rate to 50 beats before the onset of ventricular fibrillation at one time was accompanied by similar transitions, as has been described, only at a higher rate of both the auricles and ventricles.

3 Schwartz, S. P. The Action of Digitalis in Complete Heart Block, Its Toxic Influence on the Idio-Ventricular Rate and Rhythm, *Am Heart J* 4: 408, 1929.

4 All these studies were carried out on lead 2 only.

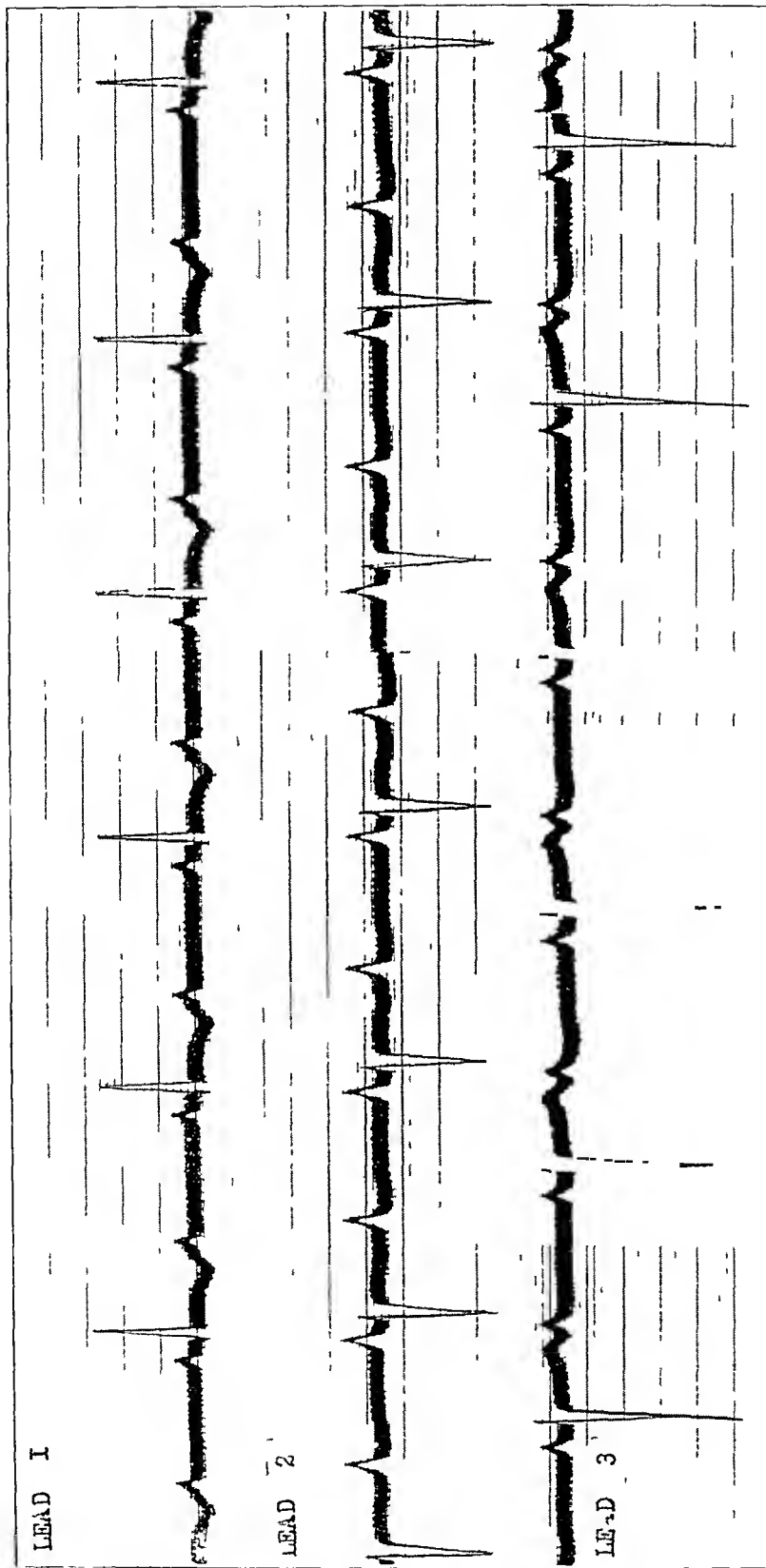


Fig 2—Apparent partial heart block with a regular ventricular rate of 42.8 beats and an auricular rate of 83.3 The main ventricular deflection was downward in lead 2, as compared with the previous record

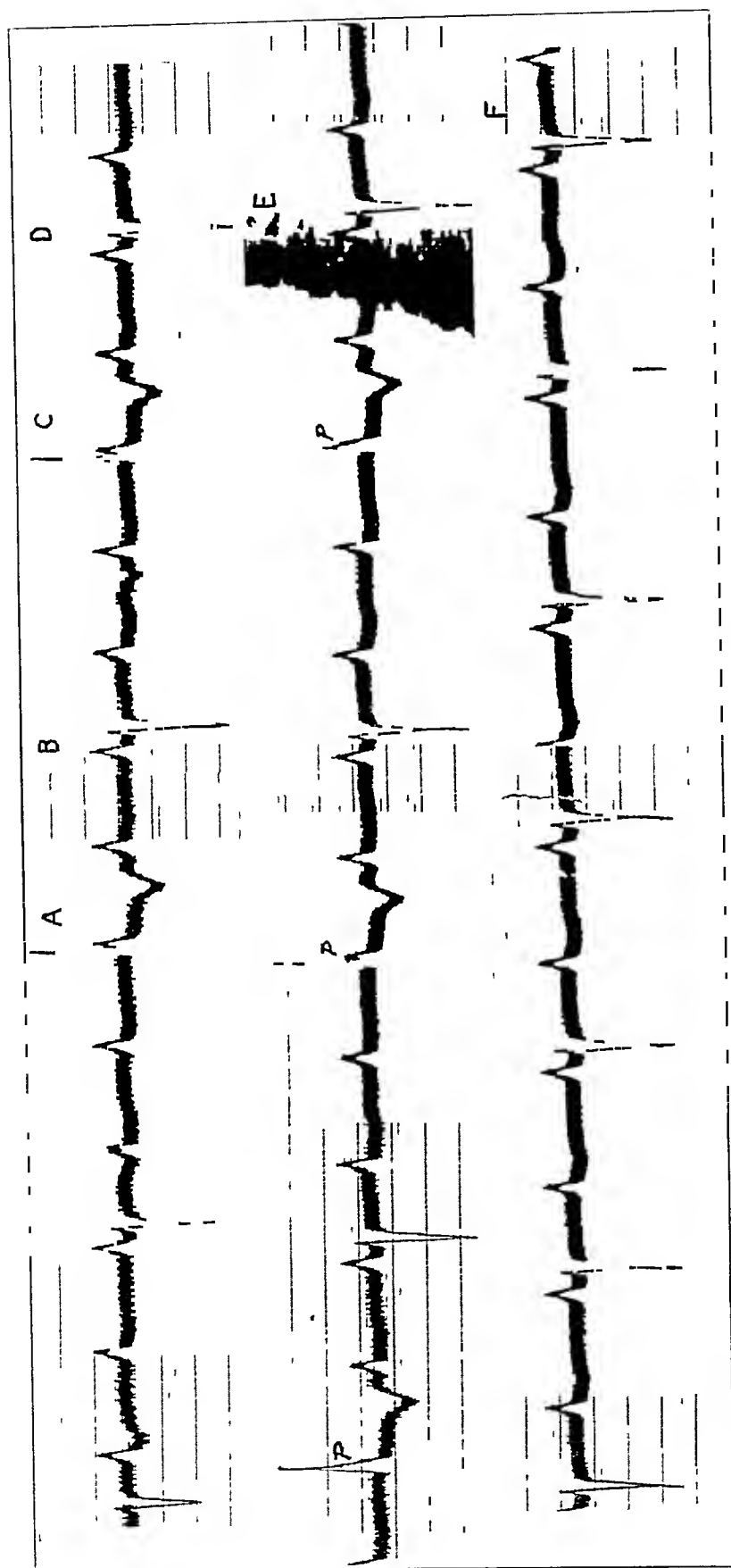


Fig 3—Continuous strip, lead 2 only This record was obtained twenty minutes after the preceding one At first, the auricular rate was inconstant and averaged 103.4 beats per minute The ventricular rate was also inconstant, there being a 5:2 block between A and E A bigeminal rhythm was produced by the simultaneous contraction of each third auricular beat with that of the ventricles At such times the main ventricular complex was upward instead of downward At E there was a change from a 5:2 block to a 2:1 block, with a concomitant reduction in the auricular rate of 93.7

On several occasions, it was possible to register seizures of paroxysmal ventricular fibrillation coming in rapid succession at intervals of from one-half to one minute, the patient alternately regaining consciousness with the restoration of the basic ventricular rhythm. At such times the ventricular rate, when recorded between the attacks and pre-



Fig 4—Continuous strip, lead 2 only. *A*, the end of a seizure of transient ventricular fibrillation, *B*, the postundulatory pause, *C*, the onset of the intermediary idioventricular rhythm, *F*, the establishment of the basic ventricular rhythm, *G*, a premature beat initiating the tachysystolic stage (*G-I*) preceding another seizure of transient ventricular fibrillation

ceding a period of syncope, averaged 50 and 62.5 beats, respectively, per minute, and was almost regular for long periods at a time (fig 4 *F-G*)

In short, a paroxysm of ventricular fibrillation was always preceded by a gradual acceleration through steplike progressions of both the basic auricular and ventricular rate, the highest regular ventricular rate recorded being 65.2 beats per minute.

In addition to these increasing variations in the rate of the dominant auricular and ventricular rhythm, premature beats of a distinct type and appearing at first alternately, so as to form a bigeminal rhythm, began to disturb the regularity of the heart. The electrocardiograms reveal that these extrasystoles invariably and uniformly arose from the same focus (fig 4 *G* and fig 5 *B, D*). Both the Q-R-S complexes as well as the T waves are distinctly different in size, shape and form from those of the dominant ventricular beats.

When the main complexes of the basic ventricular rhythm are dextrograms instead of levograms, these initial alternate extrasystoles assume a slightly different form, but they are of the same character when the phenomenon is repeated, their voltage and duration being almost the same, the intervals measuring slightly less or more than twelve hundredths of a second (fig 6 *B, C, D, E*).

The electrical deflections that follow these alternate extra beats, so as to increase further the ventricular rate and disturb the regular rhythm, are very variable from time to time.

The onset of their appearance is also variable. Frequently, only two extra beats are added to the bigeminy, and this sequence of events is repeated as such or is occasionally interrupted by a trigeminal or polygeminal rhythm coming at almost regular intervals after 2, 3 or 4 regular auricular beats precede it (fig 5 *B-C* and fig 6 *E-F*).

Infrequently, groups of from 5 to 10 beats would disrupt this rhythm, each extra beat so superimposed on the other as to distort the contour of the main ventricular deflection (fig 5 *D-E* and fig 6 *B*). The auricular sequence does not appear to be disturbed during these short runs of superimposed ventricular beats. Clinically, at such times, the patient was never observed to have lost complete consciousness.

While such short runs of from 5 to 10 beats were observed to disturb the rate and rhythm for hours at a time, ventricular fibrillation with definite syncope was not ushered in unless the basic ventricular rate as well as the auricular rate had definitely increased independent of the presence of premature beats.

ALTERATIONS IN THE ELECTROCARDIOGRAM DURING VENTRICULAR FIBRILLATION

The onset of every recorded seizure of ventricular fibrillation in the patient was initiated (comparisons are made of lead 2 only) by a ventricular extrasystole that was always of the same character and appar-

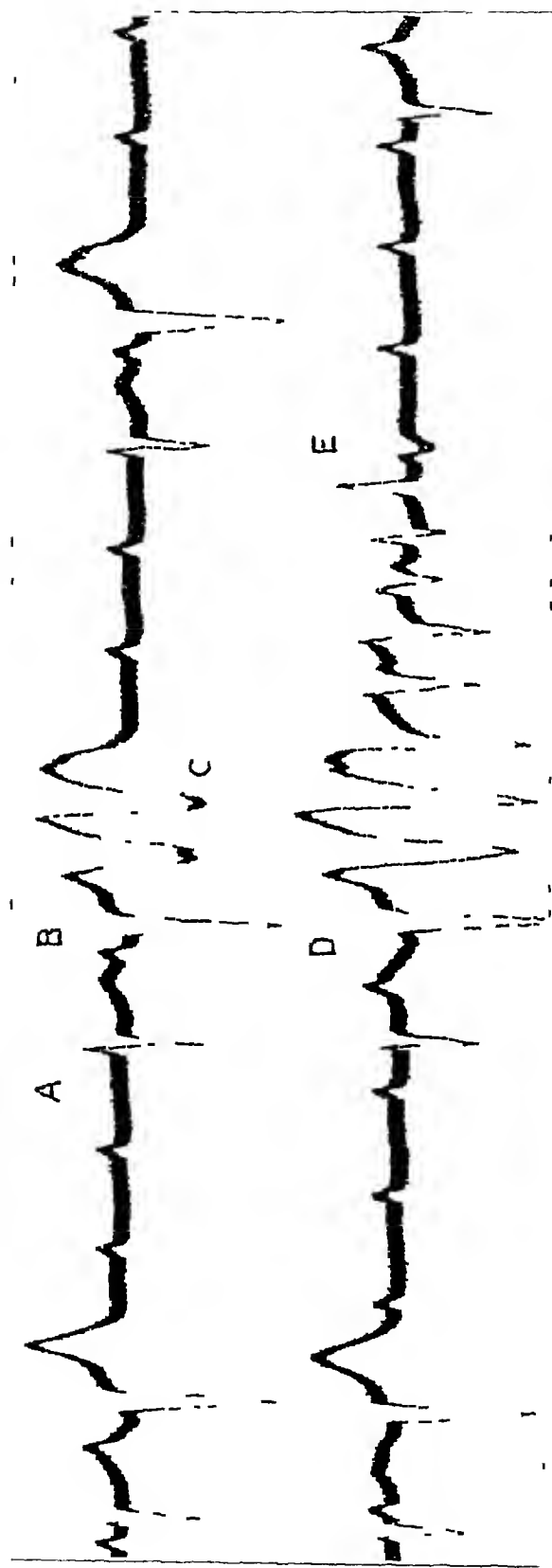


Fig 5—Continuous strip, lead 2 only The main ventricular deflection is a levocardiogram, periods of reexcitation consisting of a succession of ventricular beats, superimposed on each other so as to increase the ventricular rate of 300 beats per minute Note that the initial ventricular deflection initiating these short runs is always of the same shape, size and form

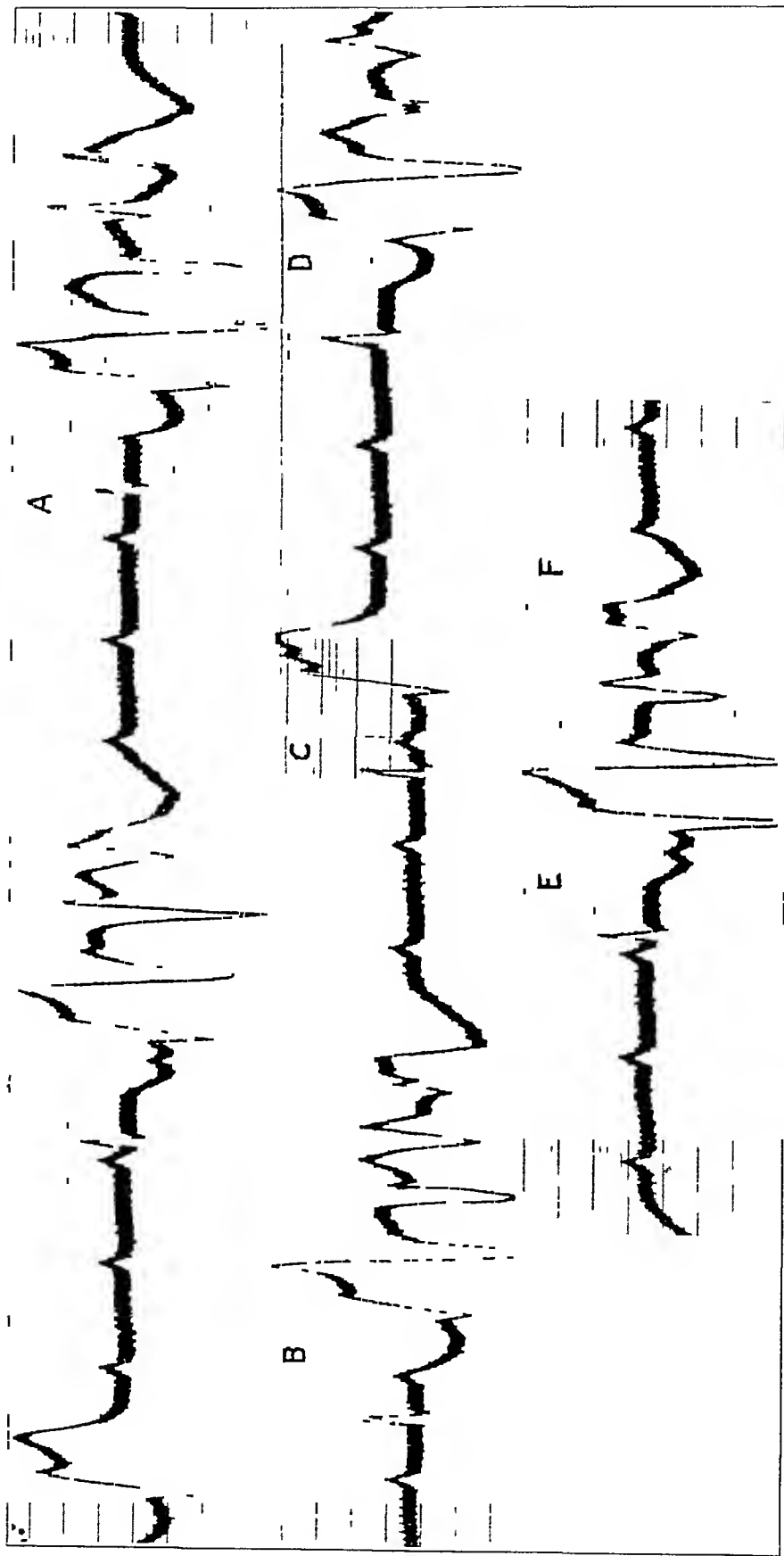


Fig 6—Continuous strip, lead 2 only The main ventricular deflection is a dextrocardiogram Recurrent groups of ventricular beats interrupted a slow basic ventricular rate Note that the premature beat initiating each group is always of the same shape and form The auricular rate of 115.3 beats was regular and not disturbed by the periods of ventricular reexcitation The patient complained of dizziness and spots before the eyes at such times

ently arose from the same focus in the ventricle. This deflection, measuring 0.12 second and accompanied by an unusually large T wave, was followed by a series of Q-R-S complexes, one superimposed on the other, which for 2 or 3 beats at the most were of large size (fig 4 G). Sometimes this extrasystole would be followed for several beats by complexes similar in form to it but smaller in amplitude. A sudden increase in the ventricular rate to approximately 120 beats would then continue for eight or ten seconds before the appearance of smaller, more regular and faster oscillations. This "tachysystolic" stage immediately preceding ventricular fibrillation was due to a ventricular arrhythmia with deflections that appeared to arise from multiple foci of the ventricles.

On one occasion a period of unconsciousness with epileptiform seizures lasting over four minutes was initiated by an irregular ventricular tachycardia with a rate of 125 beats per minute, lasting for 26.2 seconds before ventricular fibrillation set in. The ventricular complexes of this "tachysystolic" stage, although lower in amplitude, resembled very closely the usual initial ventricular extrasystoles associated with the onset of ventricular tachysystole or fibrillation (fig 8 B-C).

During a typical major period of syncope accompanied by epileptiform seizures, the rate of the ventricular oscillations varied from a minimum of 250 beats per minute to a maximum of 1,000 beats. The oscillations during this period differed from each other in amplitude and duration and there was a periodic waxing and waning of the electrical deflections, some of the waves being greater in voltage than those of the basic ventricular deflections (fig 7).

This phasic variation in the deflections of the electrocardiograms persisted until the end of the syncopal attacks.

A few seconds before ventricular fibrillation ceased, however, the oscillations increased in amplitude, reaching at times a voltage of 30 mm, the deflections became wider and more irregular, some being 0.4 second in duration, they were distinctly separated from each other by a short interval, and then an abrupt change in the mechanism followed (fig 9, lead 1 and fig 10 B).

MODE OF RECOVERY FROM VENTRICULAR FIBRILLATION

Two distinct modes of recovery from ventricular fibrillation were observed. In one type, the fibrillation ceased promptly and was followed by a postundulatory pause varying from 0.8 second to 1 second (fig 4 B). The basic ventricular rhythm did not appear, however, for several seconds after this and it was preceded by an idioventricular rhythm, with a slightly irregular rate averaging 60 beats per minute.

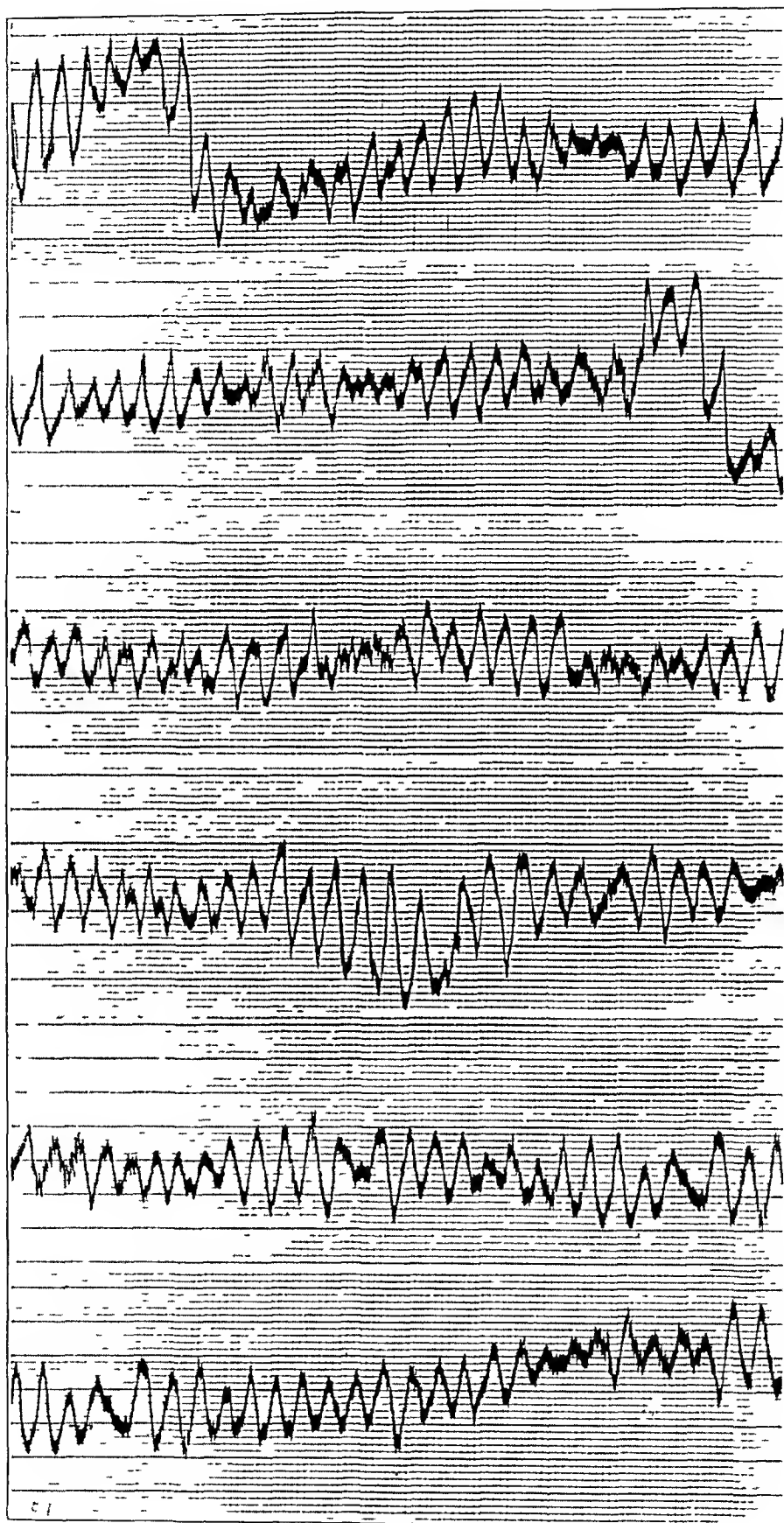


Fig 7—Continuous strip, lead 2 only. Record obtained during a period of unconsciousness. The ventricular rate varied from 300 to 1,000 beats per minute. There was periodic waxing and waning of the atypical ventricular complexes.

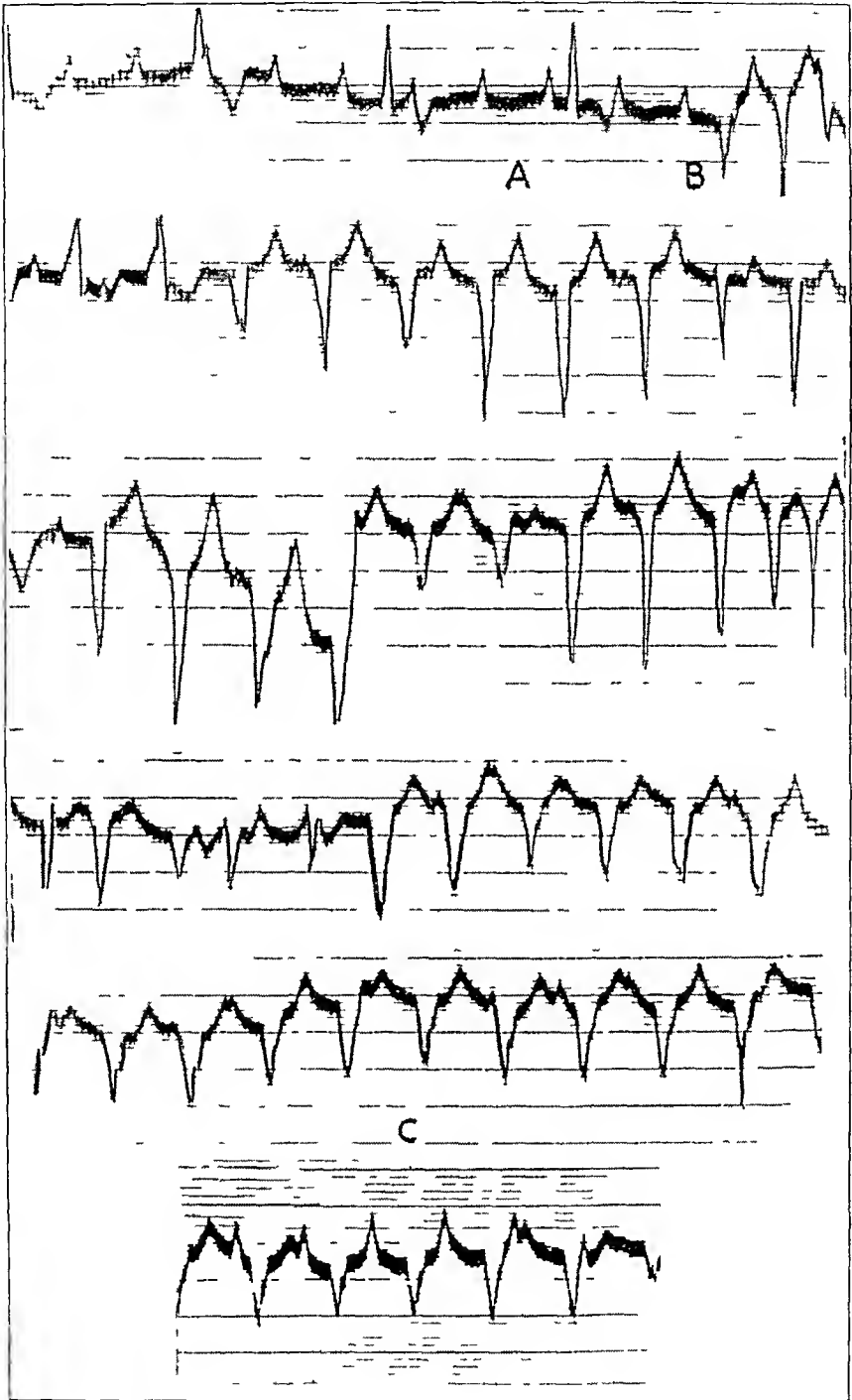


Fig 8—Continuous strip, lead 2 only A period of tachysystole with a slightly irregular ventricular rate of 150 beats per minute followed a basic ventricular rate of 65.2 beats and preceded a transient seizure of ventricular fibrillation The auricular rate kept pace with the ventricular in this stage

Although the initial beat of this idioventricular rhythm was occasionally different (fig 4 C), the complexes forming this rhythm were usually all of the same form. They were wide deflections with abnormally large T waves, some of which increased progressively in size (fig 4 D-E)

The second type of recovery was also sudden, but was not followed by a postundulatory pause. A careful study of such a record of recovery reveals an idioventricular beat initiating an idioventricular rhythm with ventricular complexes totally different from those of the

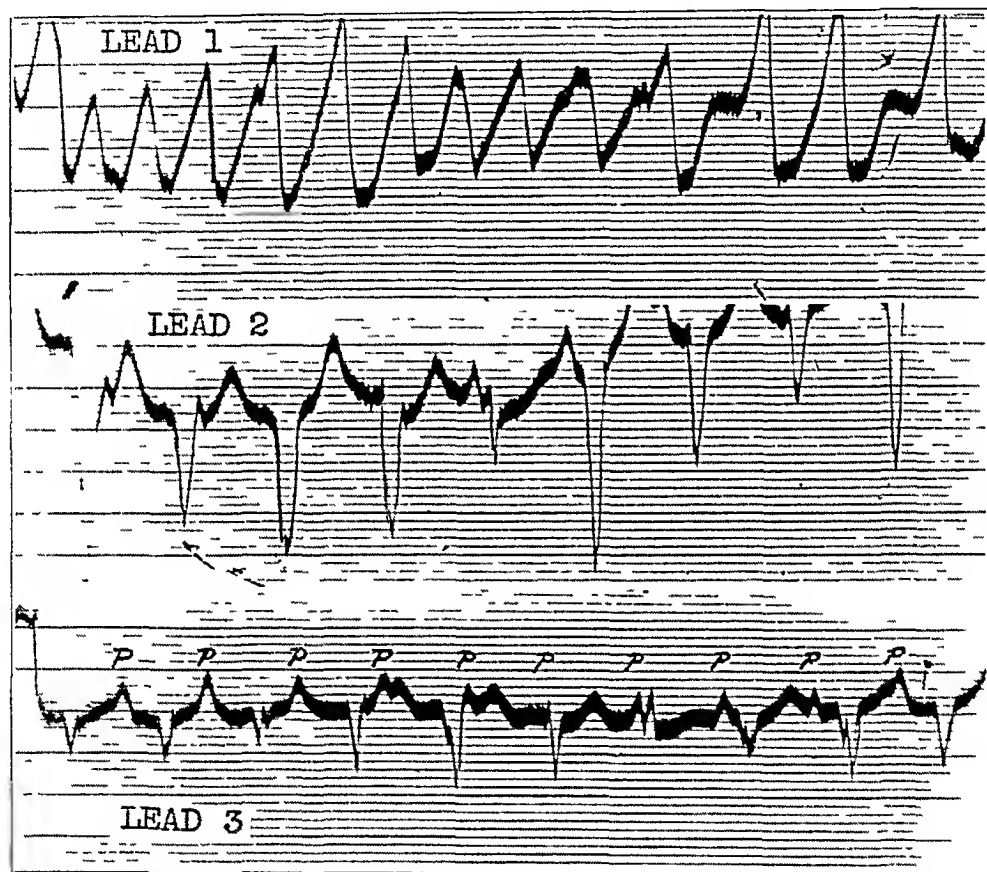


Fig 9—Three leads taken in rapid succession. The end of a period of transient ventricular fibrillation, best seen in lead 1, was followed by a tachysystole of 160 beats per minute prior to revival of the normal mechanism

dominant and basic rhythm (fig 10 B). A postundulatory pause is not visible since an idioventricular beat is seen to arise from the last of the waves terminating the ventricular fibrillation.

As in the previous type of recovery, this rhythm, averaging about 60 beats per minute, lasted only from nine to twelve seconds before the appearance of the basic ventricular rate, which was always high (60 to 90 beats per minute) even in the presence of complete auriculo-ventricular dissociation. The onset of the dominant rhythm seems to have some definite relationship to the appearance of auricular con-

tractions (fig 4 *E-F*) Complete restoration of the usual rhythm following ventricular fibrillation was observed to come after three successive auricular contractions appeared subsequent to an idioventricular beat

On one occasion transition from ventricular fibrillation to the basic rhythm was gradual, and it was interrupted by a tachysystolic stage with a ventricular rate of 120 beats per minute, the ventricular complexes of

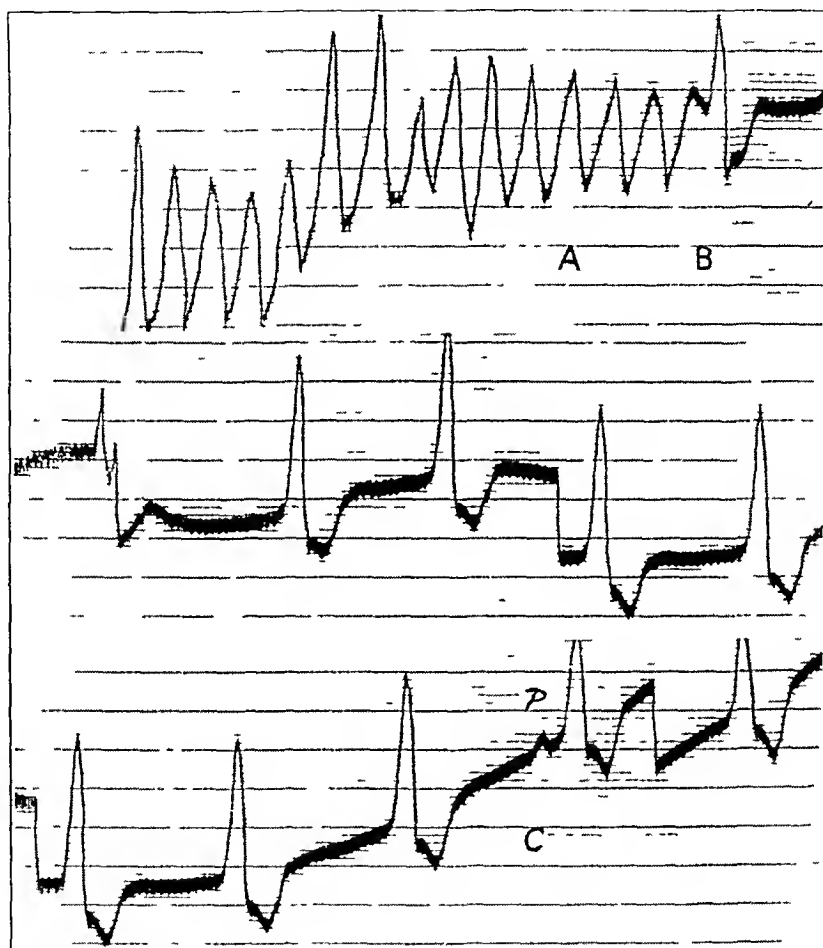


Fig 10—Continuous strip, lead 2 only Record obtained at the end of a period of unconsciousness which coincided with cessation of a seizure of transient ventricular fibrillation The intermediary idioventricular rhythm preceding the development of the basic ventricular rate may be seen between *B* and *C*

which varied in size, shape or form from beat to beat The auricular rate during this period of recovery kept pace with the ventricular rate, and restoration to the basic rhythm took place as in the previous recoveries, the dominant beat appearing after three successive auricular beats (fig 9, leads 1, 2 and 3)

When clinical and graphic correlations were made, the return to consciousness coincided with the termination of the ventricular fibrilla-

tion and the appearance of either the idioventricular rhythm or the post-fibrillation period of tachysystole

COMMENT

These observations reveal that syncopal seizures in patients with auriculoventricular dissociation may result from ventricular fibrillation. A few such cases are recorded in the literature⁵ It is of particular interest to note that the mechanism responsible for the syncopal attacks in this case was always of the same nature when recorded, namely, ventricular acceleration instead of ventricular standstill, which has been observed in others It is most likely that the other unrecorded seizures observed in this patient were also of the same nature and not due to ventricular standstill, for the premonitory periods and periods of recovery noted clinically resembled each other very closely and were similar to those recorded In this instance every syncopal seizure, whether recorded graphically or studied clinically, was preceded by a definite progressive increase in the basic ventricular rate from an average of 38 beats per minute to as high as 65.2 beats Consequently, the erroneous impression gained from some studies⁶ that syncopal seizures never occur in patients with auriculoventricular dissociation if the established ventricular rate is greater than 25 beats per minute should be discarded

It is very likely that this gradual increase in the regular ventricular rate with steplike progressions is a necessary precursor in the mechanism responsible for the development of ventricular fibrillation in this patient

There is experimental evidence that the ventricles are able to assume a higher rate of rhythm more readily if this rate is approached gradually than if it is approached abruptly It has been shown by Mines⁷ that with increasing frequency of stimulation, each wave of excitation in the heart muscle is propagated more slowly, but lasts a shorter time at any one point in the muscle The wave of excitation becomes slower and shorter Similarly, the refractory phase is shortened It follows that by gradual acceleration, the ventricles can be caused to beat at a higher rate than if the rate of stimulation is abruptly raised

While the experimental evidence for this phenomenon is based on the increase in the ventricular rate during the presence of sinus rhythm, I have also observed it in a patient with complete auriculoventricular dissociation following the administration of toxic doses of digitalis³

5 Davis, D, and Sprague, H B Ventricular Fibrillation Its Relation to Heart Block, *Am Heart J* 4 559 (June) 1929

6 Read, J M Complete Heart Block, Roentgen-Kymographic Study, *Arch Int Med* 45 59 (Jan) 1930

7 Mines, G R On Dynamic Equilibrium in the Heart, *J Physiol* 46 34, 1913

In a woman with complete heart block and a basic ventricular rate of 37.3 beats per minute, the sequence of events after the use of digitalis in more than the "average therapeutic dose" was almost exactly the same as the premonitory period observed in the patient whose case is herewith reported when this period was studied prior to the onset of a seizure of transient ventricular fibrillation.

At first, there was an increase in the ventricular rate from 37.3 beats per minute to 48.4 beats. From then on the increase in the idioventricular rate was progressive, until it reached 65.2 beats per minute, independent of the presence of any premature beats. On several occasions in this period of gradual acceleration, the electrocardiograms revealed abrupt changes from a complete auriculoventricular dissociation to what appeared as 2:1 partial heart block, and this was invariably accompanied by a transition of the Q-R-S complexes from a dextrocardiogram to a levocardium and vice versa, as the ventricular rate progressively increased. In the meantime, at a point where the basic ventricular rate averaged 53.5 beats, extrasystoles of an unusual type, with high voltage and wide deflections, began to interrupt the regular basic rhythm. At first these appeared alternately so as to form a bigeminal rhythm, but as the drug became more effective and the basic rate was accelerated, groups of beats began to disrupt the regular rhythm. These came in series of 2, 3 and 4 at a time, and resembled closely the periods of reexcitation seen in the accompanying records (fig. 5 B).

Unfortunately, observations on this particular patient had to be discontinued because of the onset of systemic toxic manifestations. There is good reason to believe, however, from other personal observations on similar patients with complete heart block, that ventricular fibrillation following the use of toxic doses of digitalis always appears after the basic ventricular rate has been gradually accelerated.

It is obvious from a study of innumerable electrocardiograms taken in both instances that the transitions from a lower ventricular rate to a higher one, with the accompanying variations in rhythm, are always initiated by an extrasystole. These extrasystoles initiating a new rhythm during the premonitory period are all of the supraventricular type (fig. 3 E). The extrasystoles initiating the periods of ventricular fibrillation, however, are always abnormal and are of an extremely wide deflection (figs. 5 and 6 B). This has also been observed experimentally, when transitions from one rate of the ventricles to another have been induced by a suitably placed extrasystole.⁷

Both the progressive increase in the rate of the beating of the ventricles, whether spontaneous or induced by digitalis, as well as the fact that the onset of each period of ventricular fibrillation observed in these studies was initiated by a distinct type of stimulus (an extra-

systole of a particular type) or the last of almost successive similar stimuli (fig 4 *G, H*), as has been observed experimentally,⁸ support the hypothesis that a circus movement underlies the mechanism of ventricular fibrillation⁹

Further progress in such studies would be of value if there was a more intimate knowledge of the factors responsible for the spontaneous acceleration of the ventricles in patients with auriculoventricular dissociation subject to transient periods of ventricular fibrillation

The present observations are still too meager to attempt a classification of the various stages of the fibrillatory contractions of the ventricles as pictured in the electrocardiograms. The drawbacks to such graphic interpretations have recently been well pointed out by Wiggers,¹⁰ and the fact that most of the appended records were taken with lead 2 only is the more reason for postponing this phase of study and a comparison of these records with those obtained in animals

It will suffice to state that the longest period of syncope observed in this case, that is, six minutes and two seconds, with spontaneous revival following it, as confirmed by the electrocardiograms, was associated with an acceleration of the ventricles that does not resemble very closely records of ventricular fibrillation observed in animals

Of particular importance, in the light of recent researches,¹¹ was the mode of spontaneous recovery of the heart observed in this patient. At times fibrillation ceased promptly, a postundulatory pause followed, and revival was initiated by an idioventricular rhythm. Even when a postundulatory pause was not to be seen, recovery took place through the intermediary idioventricular rhythm, with impulses originating in a focus different from that of the basic ventricular rhythm. This sequence of events may bear some relationship to future studies in the therapy for ventricular fibrillation in man, since recovery somewhat similar in type to this mechanism has been seen by Wiggers¹⁰ to follow the use of calcium with massage after all movements have ceased in a heart in which ventricular fibrillation had been induced experimentally by the intracardiac injection of potassium chloride solution

8 Mines, G. R. On Circulating Excitations in the Heart Muscles and Their Possible Relation to Tachycardia and Fibrillation, *Tr Roy Soc Canada*, ser 3 8 43, 1914. Levy, A. G. The Relation Between Successive Responses of the Ventricle to Electric Stimuli and Ventricular Fibrillation, *J Physiol* 49:54, 1914.

9 Mines (footnote 7). Garrey, W. The Nature of Fibrillary Contraction of the Heart, Its Relation to Tissue Mass and Form, *Am J Physiol* 33 397, 1914.

10 Wiggers, C. J. Studies of Ventricular Fibrillation Caused by Electric Shock. II Cinematographic and Electrocardiographic Observations of the Natural Process in the Dog's Heart, Its Inhibition by Potassium and the Revival of Coordinated Beats by Calcium, *Am Heart J* 5 351, 1930.

11 Wiggers, C. J. Studies on Ventricular Fibrillation Produced by Electric Shock. III The Action of Antagonistic Salts, *Am J Physiol* 93 197, 1930.

SUMMARY

1 A study was made of the electrocardiograms of a patient with auriculoventricular dissociation, who suffered from sixty-seven seizures of unconsciousness during a period of seven months while she was at the Montefiore Hospital

2 Each syncopal seizure was associated with periods of ventricular fibrillation. The longest recorded attack with spontaneous recovery lasted six minutes and two seconds

3 The alterations in the electrocardiograms preceding a syncopal seizure consisted of a gradual acceleration through steplike progressions of both the basic auricular and ventricular rates, the highest regular ventricular rate recorded being 65.2 beats per minute before ventricular fibrillation set in

4 Periods of reexcitation of from 4 to 11 beats at a time were observed to appear during the premonitory period, heralding the approach of a seizure of unconsciousness

5 The onset of every recorded seizure of ventricular fibrillation in this patient was initiated by a ventricular extrasystole which was always of the same character and arose from the same focus in the ventricle

6 The ventricular rates during the periods of ventricular fibrillation varied from a minimum of 250 to a maximum of 1,000 beats per minute

7 Spontaneous revival usually coincided with cessation of ventricular fibrillation. The mode of recovery was variable, but the restoration of the basic rhythm was preceded by an idioventricular rhythm, with a slightly irregular ventricular rate following, as a rule, a postundulatory pause

8 Periods of unconsciousness in patients with auriculoventricular dissociation are associated with transient seizures of ventricular fibrillation much more commonly than has been suspected hitherto

9 A clinical diagnosis of transient ventricular fibrillation may be suspected in such patients, if preceding a period of unconsciousness the heart rate has been noted to increase above that of the usual basic rate

CHRONIC ARTHRITIS

WITH SPECIAL REFERENCE TO INTRAVENOUS
VACCINE THERAPY *

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AND

B J CLAWSON, M D

MINNEAPOLIS

Much difference of opinion exists concerning what chronic joint diseases should be included in the term chronic arthritis. There are the changes, mostly proliferative, which from the anatomic appearance might well be considered infectious in nature. The relation of an infectious process to the joints showing retrogressive changes in the bone and cartilage is not so evident. Nichols and Richardson,¹ however, noted a decided overlapping in these two processes. The question arises whether the various anatomic proliferative and degenerative changes noted in nonspecific joint disease may not be different manifestations of a common injury. The finding of an etiologic agent would help in clearing up the concepts of chronic joint diseases. If an organism could be shown to have an etiologic relationship to the various anatomic forms of joint disease commonly called chronic arthritis, experiments toward combatting this organism could be started. With these ideas in mind and considering the recent experiments relative to intravenous vaccination in acute rheumatic fever,² the present work was started.

The purpose of the work reported in this paper was to study a series of patients with chronic arthritis in respect to classification, etiology and intravenous vaccine treatment. The chief emphasis was placed on the vaccine treatment.

MATERIAL

The patients were from the outpatient department of the University of Minnesota Hospital. In selecting cases for arthritic study, one chief criterion (joint pains) was followed. It was considered necessary that

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* From the Department of Medicine and the Department of Pathology, University of Minnesota

1 Nichols, F. H., and Richardson, F. L. Arthritis Deformans, J. M. Research **21** 149, 1909

2 Clawson, B. J. Experiments Relative to a Possible Basis for Vaccine Therapy in Acute Rheumatic Fever, J. Infect. Dis. **49** 90 (July) 1931

the joint pains should have been present almost constantly for at least several months preceding the admission for treatment. In most cases, the pain had been present from one to twenty years. In nearly all, multiple joints were involved. The patients ranged in age from 18 to 78 years. The great majority showed joint involvement demonstrated by physical and roentgen examinations. Before the vaccine treatment was begun, most patients had the following examinations: A complete physical examination, including a Wassermann test and blood and urine studies, a roentgen examination of one or more joints, blood culture, a test for the agglutination titer of the serum with *Streptococcus viridans*, and an intracutaneous skin test with a suspension of *Streptococcus viridans*. One hundred patients with chronic arthritis have been treated up to the present time.

CLASSIFICATION

There has been much discussion of the etiology and classification of a large group of pathologic joint conditions. The etiologic factor has been well accepted in such cases as tuberculous, syphilitic, gonorrheal, traumatic and gouty joint involvement. Other joint conditions have met with much less universal agreement as to etiology and classification. This lack of agreement is illustrated by the following classifications commonly used:

British	American
I Rheumatic fever	I Rheumatic fever
II Rheumatoid	II Proliferative Infectious (roentgen) Atrophic
III Osteo-arthritis	III Degenerative Hypertrophic (roentgen)

Most authors have tended to draw a sharp line between rheumatic fever and the other arthritides. The chief causes for division have been (1) the tendency of rheumatic fever to be complicated by endocarditis, which rarely occurs in more chronic forms of arthritis, (2) the tendency of the joint involvement in rheumatic fever to subside without obvious permanent damage. Many cases of so-called rheumatoid arthritis (proliferative infectious, atrophic) are difficult to distinguish clinically from rheumatic fever. In some cases clinicians may wait several weeks or several months before making a diagnosis. The final diagnosis is influenced by the persistence of joint involvement or the presence of an endocarditis. A few patients with typical clinical rheumatic fever and, in some instances, an associated endocarditis may manifest progressive chronic joint disease. In our series we are unable to place a number of patients definitely in the accepted classifications, and we see a gradual graduation in clinical types from those termed

rheumatic fever to those termed degenerative arthritis. If the active infection has subsided the clinical manifestations are different than when the infection is persisting as it is in our series.

The roentgen findings in our series have shown all types of change. The degree of roentgen involvement cannot be taken as a definite guide of the clinical severity of a given case. The changes shown by roentgenography are much less marked in relation to the clinical condition present in younger than in older patients. Marked new bone formation is infrequent in young arthritic patients, while involvement of the synovial membrane and periarticular tissues is usually prominent. Secondary muscular atrophy often plays a prominent rôle in the disability present in many persons with arthritis, and this too is not evident from roentgen examination. The active infectious process in certain young patients may of itself clear up and leave them crippled for life with capsular and periarticular changes and muscular atrophy. In such a case there would probably never be new bone formation or a change in the roentgen appearance, even though the patient might live many years, unless a reinfection were to take place in later life. Later, under case reports there will be given detailed roentgen findings in correlation with the clinical pictures present in persons with positive blood cultures. Roentgenography, while of definite value in determining certain types of joint damage, has also added to the general confusion of classification of joint disease.

ETIOLOGY

At present there is a decided lack of agreement in opinion concerning the etiology of chronic arthritis. Recent work strongly suggests the streptococcus as the active agent. In 1920, Richards³ cultured the blood of 114 persons with chronic arthritis. *Streptococcus viridans* in pure culture was found in 14 (12.2 per cent).

Cecil, Nicholls and Stainsby⁴ in two reports (1929 and 1931) stated that they had recovered streptococci from the blood of patients with chronic arthritis. In their last series of 154 cases of rheumatoid arthritis, they obtained streptococci from the blood in 96 cases (62.3 per cent). They also obtained streptococci from the joints in 33 of 49 cases (67.3 per cent).

In our series, blood cultures were obtained in 57 cases of unselected types of chronic arthritis and from 50 normal persons. The blood of both arthritic and normal persons was cultured in the same incu-

³ Richards, J. H. Bacteriological Studies in Chronic Arthritis and Chorea, *J. Bact.* **5** 511, 1920.

⁴ Cecil, R. L., Nicholls, E. E., and Stainsby, W. J. The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, *Arch. Int. Med.* **43** 571 (May) 1929, The Etiology of Rheumatoid Arthritis *Am. J. M. Sc.* **181** 12, 1931.

bator and examined in the same manner. The examiner had had no knowledge of the histories of the cases and could not, therefore, be prejudiced in the search for organisms. The blood of the normal persons was cultured as a control against contaminations from the air and the skin and to determine whether streptococci might be found frequently in blood cultures of all persons.

The technic⁵ was the same as that used previously in culturing blood from patients having acute rheumatic fever. In 7 of the 57 cases of chronic arthritis, staphylococci were found in the blood cultures. Streptococci in pure culture were found in 25 of the remaining 50 cases (50 per cent). A positive streptococcus culture was obtained from one of the 50 normal persons (2 per cent). This person was found later to have had a pelvic infection when the blood for culture was taken.

One of the twenty-five strains of streptococci recovered from the blood of the patients with chronic arthritis was a typical hemolytic streptococcus. The remaining twenty-four either were of the viridans type or were inactive on the blood agar plate. They do not represent a special strain type. The organisms were seldom found in the culture mediums before the fifteenth day of incubation, and in some cases between the twenty-fifth and thirtieth days.

Our bacteriologic observations agree with the work of Cecil, Nicholls and Stainsby⁴ in suggesting that the streptococci are an important etiologic factor in chronic arthritis.

IMMUNE REACTIONS

Two types of immune reactions (agglutinin and intradermal skin tests) to streptococci were studied in the patients with chronic arthritis. A comparison of these reactions was made in the arthritic patients before and after treatment.

The serums of 74 patients with chronic arthritis were tested for streptococcic agglutinins. The organism used was a strain of *Streptococcus viridans* isolated from the blood of a patient with acute rheumatic fever. A weak saline suspension of the organisms was mixed with increasing dilutions of the patient's serum in Wassermann tubes. The tubes were incubated in a water bath at 40 C for two hours. The tubes were then removed from the bath and allowed to stand in a cool place for from eighteen to twenty hours, when the degree of agglutination was determined. The blood of all patients was tested before treatment was begun, and at the end of the course of treatment.

⁵ Clawson, B. J. Studies on the Etiology of Acute Rheumatic Fever. *J. Infect. Dis.* **36**: 444 (May) 1925.

The initial streptococcic agglutinating titer of the serums of 74 patients before treatment was found to average 1 132. The average titer after a course of treatment was 1 11,525. It is to be noted that the intravenous vaccine treatment brings about a decided rise in the concentration of agglutinins in the patient's serum.

Intradermal skin tests were made with the same strain of streptococcus that was used for agglutinating tests. Skin tests have been used by a number of persons in rheumatic fever and chorea, scarlet fever, measles, nephritis and chronic arthritis. Different strains of *Streptococcus hemolyticus* and *viridans* have been used by different investigators. Birkhaug⁶ tested rheumatic, arthritic and normal persons with bacterial suspension, autolysates and filtrates of several streptococci of rheumatic origin. He found a higher percentage of positive tests in patients with rheumatic fever and chronic arthritis than in his series of controls. Apparently the bacterial suspension gave as satisfactory tests as the other methods. We have employed a bacterial suspension in our series.

Intradermal Skin Tests with Streptococcus Viridans

Conditions	Number	Positive	Per Cent
Chronic arthritis	127	112	91.8
Controls	107	53	49.6

Two strengths of bacterial suspension were used on each patient, one of 10,000,000 killed organisms per cubic centimeter, and another of 20,000,000 in physiologic solution of sodium chloride. One-tenth cubic centimeter was injected intradermally so that there were 2,000,000 organisms in one test and 1,000,000 in the other. A control wheal of 0.1 cc of physiologic solution of sodium chloride was used in all cases. The results are shown in the accompanying table.

It is obvious from the results obtained that a positive skin test is of little significance in any individual case, but that in terms of percentages it is significantly higher in chronic arthritic patients than in a series of controls. A positive skin test probably indicates in most cases that the person is hypersensitive or allergic to the strain of streptococcus used in the test.

VACCINE TREATMENT

The application of the intravenous streptococcic vaccine therapy reported in this paper is based on previous experiments in animals,² and on the assumption that chronic arthritis for the most part is due

⁶ Birkhaug, K. E. Rheumatic Fever. Skin Hypersensitiveness of Patients with Rheumatic Fever and Chronic Arthritides to Filtrates, Autolysates and Bacterial Suspensions of Streptococci, *J. Infect. Dis.* **44** 363 (May) 1929.

to a streptococcic infection and that patients having chronic arthritis are hypersensitive to that organism. The experiments showed that animals, made hypersensitive experimentally to streptococci, could be desensitized by the intravenous injection of a streptococcic vaccine, so that such animals could be protected from the development of further lesions when given subcutaneous injections of amounts of the organism that would produce extensive lesions in nonvaccinated hypersensitive animals. The subcutaneous injection of the vaccine did not desensitize or protect the animals, but, on the other hand, made them more hypersensitive. The work of Cecil, Nicholls and Stansby⁴ and the bacteriologic observations in our 50 cases supported the etiologic significance of the streptococci in chronic arthritis. The frequency of positive skin tests in such patients suggests that they are hypersensitive to streptococci. There is an evident similarity in the etiology and hypersensitivity in the experimental hypersensitive animals and the patients with chronic arthritis. Since animals were protected, it was thought it might be possible to protect patients. With these considerations in mind, the experiments in vaccinating intravenously patients with chronic arthritis were begun. Clawson and Fahr⁷ reported on the use of intravenous *Streptococcus viridans* vaccine in the treatment for rheumatic fever. Swift and his co-workers⁸ have reported on the use of intravenous *Streptococcus hemolyticus* vaccine in the treatment for rheumatic fever.

METHOD

Intravenous injections were given to each patient at intervals of from five to seven days for the first five treatments, and at seven to fourteen day intervals for subsequent treatments. Routinely, the first dose was 100,000,000 killed organisms. The second dose in most instances was 300,000,000. The third dose was usually from 300,000,000 to 500,000,000. In most instances the dosage was reduced or held at the same amount, if the reaction following the previous injection had been severe. The fourth dose was usually from 500,000,000 to 1,000,000,000, depending on the patient's previous reaction. In some instances the dosage was not increased beyond 1,000,000,000, while in other instances as many as 3,000,000,000 or 5,000,000,000 were given. The reactions tended to be more marked with large dosage. It seems advisable now not to give more than 1,000,000,000 killed organisms.

7 Clawson, B. J., and Fahr, G. E. Experiments Leading to a Possible Basis for Vaccine Therapy in Acute Rheumatic Fever, *Proc Soc Exper Biol & Med* **27** 964, 1930.

8 Swift, H. F., Hitchcock, C. H., Derich, C. L., and McEwen, C. Intravenous Vaccination with Streptococci in Rheumatic Fever, *Am J M Sc* **181** 1 1931.

These patients were all treated in the outpatient department, and were advised to go home immediately after the injection

The following summaries of 20 cases in which the patients received vaccine therapy are inserted Ten of these had positive blood cultures and 10 negative We have included patients with and without clinical improvement while on therapy The cases have been arranged to bring out the gradation in clinical types

REPORT OF CASES

CASE 1—*History*—Mrs E P, aged 39, had had acute tonsillitis when 21 years of age (1913), and pains soon developed in most of the joints of her body Transitory swelling and redness were present in the involved joints and she had a fever She was confined to bed for three weeks Her physician made a diagnosis of "inflammatory rheumatism" Shortly afterward, he told her that a heart murmur was present Since then, she had had joint pains off and on most of the time Seven months before this report (June, 1930), her joints became much worse and remained painful She had involvement especially in her knees and fingers, and had some swelling in these joints much of the time She had been up and about for the most part, but had marked pain at times

Examination—There was a definite presystolic murmur over the apex of the heart, and the heart was enlarged, with a mitral contour There was swelling of many of the metacarpophalangeal and phalangeal joints Both knees were swollen, and the left knee was tender to pressure, as was the right wrist Roentgen examination of the right wrist was reported as follows "There is slight atrophy of the bones and some slight cartilaginous absorption, especially in the radiocarpal joint The appearance suggests an atrophic arthritis of the periarticular type with very little involvement of the joints as yet Conclusions atrophic arthritis, periarticular type" A blood culture showed *Streptococcus viridans*

Vaccine Therapy—The patient received nine injections of vaccine, in doses of from 100,000,000 to 500,000,000 organisms at weekly intervals Reactions, consisting of moderate fever and chills of a few hours' duration, came on about three hours after each injection No improvement followed the first three injections Since then, the pain has been much reduced, and she is able to do much more physical work than prior to treatment The agglutination titer was raised from 1:0 to 1:12,800 after six injections

CASE 2—*History*—In Mrs R L, aged 35, joint pains had been present for five months with swelling and redness at times This condition had progressively involved the right shoulder, hands, wrists, fingers and feet The finger involvement was transitory, there being swelling, pain and redness of four or five days' duration She had not been confined to bed

Examination—The temperature was 99.6 F No gross deformity, swelling or redness of joints was noted at this time There was some limitation of motion of the left shoulder A roentgenogram was not obtained A blood culture gave negative results

Vaccine Therapy—The patient received eight injections of from 100,000,000 to 3,000,000,000 organisms, over a period of two months On most occasions she had no reaction following the injection The first reaction followed the fifth dose of 3,000,000,000 and consisted of slight chills and fever for a few hours The joints were definitely less painful after the third injection, and the patient stated

that she felt much better generally. The agglutination titer was raised from 1:0 to 1:6,400 after six injections.

CASE 3—History—Mr. M. M., aged 22, first noticed pain in the hips and spine four years before this report. Eighteen months before, soreness developed in the right shoulder. During the past six weeks the knees had been definitely painful. He now had marked difficulty in walking and took short steps. During the past six weeks he had been sleeping very poorly because of pains, he had been unable to work the past month.

Examination—The patient was unable to extend the thighs at the hips because of pain. Tenderness was present over the hips and knees. Limitation of motion of the spine was present. Roentgen observations on the right hip and left knee were "Some suggestion of arthritis in the right sacro-iliac region, otherwise negative." A blood culture gave negative results.

Vaccine Therapy—The patient received five injections over a period of one month. The doses were from 100,000,000 to 2,000,000,000 organisms. The reactions were chiefly slight chills and fever of from two to three hours' duration. The joints were slightly improved after the second injection and much improved after the third. At that time the patient was able to return to work after being out for a month because of joint pains. The pain was practically all gone after the fourth injection.

CASE 4—History—Miss M. A., aged 18, first noticed pain in the toes of the left foot two years before this report. Since that time the feet, ankles, knees, hips, fingers, hands, wrists, elbows and shoulders had been involved. The joints had frequently been swollen, tender and warm. She had had no fever. The joints had tended to be acutely involved in succession and partially cleared up after a few days to a few weeks.

Examination—Limitation of motion was present in the left arm at the shoulder. The wrists were definitely swollen and tender to touch. There was definite limitation of motion at the wrists. The left knee and the feet were moderately swollen. Roentgen observations on the left knee and right wrist were "There is some atrophic arthritis involving the right wrist and the left knee. Slight cartilaginous destruction and some bone destruction are also present. Conclusions: atrophic arthritis, fairly marked degree, right wrist and left knee." A blood culture gave negative results.

Vaccine Therapy—The patient received twelve injections over a period of two and one-half months of doses of from 100,000,000 to 3,000,000,000 organisms. The reactions varied from none to moderate chills and fever for a few hours. There was perhaps less joint pain after two injections, and much less pain was noted after four injections. Five days after the sixth injection, the patient had pain and was unable to walk for five days because of swollen, painful ankles. The agglutination titer was depressed to 1:0 at that time. Seven hours after the seventh injection, the swelling in the feet had subsided and the patient could walk about freely. She was practically free from joint pains while under weekly injections during the following six weeks. Skin tests, positive before treatment, were very faint after five injections. The agglutination titer was raised from 1:200 to 1:6,400 after five injections.

CASE 5—History—Mrs. C. B., aged 39, had noticed multiple joint pains in the left shoulder, left hip, left foot, lower part of the spine and right temporomandibular joint for about three months (since October, 1930). No redness or swelling was seen in any of the joints. She had been working as a scrubwoman. This work had been very difficult recently because of the joint pains.

Examination—No definite swelling or deformity was present. The roentgen report was "Left ankle negative, lumbosacral spine negative." A blood culture yielded *Streptococcus viridans*.

Vaccine Therapy—Six injections ranging from 100,000,000 to 600,000,000 organisms were given at from four to seven day intervals. On two occasions there were no reactions, at other times she had chills of three to four hours' duration. She had a temperature of 102 F on one occasion. The pain in the left hip, present constantly, disappeared after the third injection, there was much less pain in all joints after four injections, and the patient was able to perform her duties as a scrubwoman much more easily. The condition was still improved after two and one-half months. The agglutination titer was raised from 1/50 to 1/6,400 after five injections.

CASE 6—History—Miss E. J., aged 27, developed a pain in the right shoulder, about nine years before this report (1922), which disappeared after a few months. She then began to have pains in her feet and hands with definite swelling, redness and local heat. Since then she had had involvement of both shoulders, elbows and knees. She continued to have joint pains. Her pain had been somewhat alleviated by a series of general diathermy treatments.

Examination—There was fairly marked deformity of both hands, owing to involvement of the phalangeal and metacarpophalangeal joints. There was almost complete fixation of the left elbow at a 60 degree angle and some fixation of the right elbow and right hip. Swelling was present over some of the joints, and there was tenderness on pressure. Roentgen examination of the left elbow was reported as follows: "There is a marked loss of cartilage, and considerable destruction, especially in the upper ends of the radius and ulna, is present. A small amount of new bone formation has also taken place, but this is minimal. Conclusion: chronic atrophic arthritis." A blood culture yielded *Streptococcus viridans*.

Vaccine Therapy—Twelve injections were given at one week intervals. The dosage was run up from 100,000,000 to 1,000,000,000 organisms in four injections. It was then reduced to 300,000,000 for subsequent treatments. Reactions varied from very slight reactions to chills and fever for four or five hours, and increased aching for twenty-four hours after the injection. The joints remained about the same throughout with the usual fluctuation in pain. The skin tests, positive before treatment, became negative. The agglutination titer was raised from 1/800 to 1/25,000 after six injections.

CASE 7—History—Mrs. A. J., aged 43, first noticed swelling and pain in both knees one year before this report (January, 1930), no redness was present. The pain had been present constantly and was aggravated by walking. Six months later her fingers became similarly involved, and she also had pain through her arms. The past three or four months she had noticed swelling and pain in the feet and ankles. At the time of examination the pain was most marked in the fingers and hands.

Examination—Both wrists were slightly enlarged, the left more markedly, they were very tender on pressure. Local swelling appeared over many of the finger joints. The other joints were tender on pressure but showed no gross deformity. Roentgen observations on the right hand were: "Slight to moderate atrophy of the bones, no particular involvement of the joints themselves. The appearance would suggest a slight amount of periarticular arthritis." A blood culture gave negative results.

Vaccine Therapy—The patient received eleven injections over two and one-half months, ranging from 100,000,000 to 2,000,000,000 organisms. On some

occasions there were no reactions, again there were moderate chills and fever of from thirty minutes to three hours' duration. The joints were less painful after four injections. Since then they have remained definitely less painful than before therapy, though with some exacerbations. The agglutination titer was raised from 1:0 to 1:400 after six injections.

CASE 8—History—Mrs. M. H., aged 61, had had pains in many joints since 10 years of age. These had been much worse during the past seven years (since 1924). She now had pain and swelling in the hands and fingers, elbows and left shoulder and over the cervical spine, these symptoms were most marked in the right hand and elbow.

Examination—There were definite swelling and slight fluctuation of the right elbow, limitation of movement and marked pain were noted on movement. Some swelling and tenderness were present in some of the right finger joints and there was tenderness over the right hand. Motion of the right wrist was painful. Roentgen observations on the right elbow were: "There is some atrophy of the bones about the elbow joint and also a few very small spurs. There is only very slight narrowing of the joint space itself, the change being chiefly periarticular. Conclusion: arthritis of right elbow joint, periarticular type." A blood culture gave negative results.

Vaccine Therapy—The patient received seventeen injections over a period of nearly four months at five to ten day intervals. The doses were from 100,000,000 to 500,000,000 organisms. Reactions were present after most injections, usually chills and fever of from three to six hours' duration. Nausea occurred with some reactions. No definite relief was consistently present. Periods of possible improvement occurred. Intradermal skin tests showed nodules which persisted for six weeks. Skin tests, applied after six injections, were negative. The agglutination titer was raised from 1:400 to 1:12,800 after seven injections.

CASE 9—History—Mrs. E. M., aged 61, had had joint pain for the past forty years. This had been present in nearly all of her joints, although there had never been any redness or swelling. Recently she had had marked pain in the knees and some swelling at times.

Examination—Moderate swelling of the knees was observed. There were no gross deformities of any joints. Roentgen examination of the left knee was reported as follows: "Slight evidences of static arthritis are present, but no other evidence of pathology. Conclusion, slight static arthritis." A blood culture gave negative results.

Vaccine Therapy—The patient received thirteen injections of from 100,000,000 to 3,000,000,000 organisms over a period of nearly four months. Most of the reactions consisted of slight chills and fever for two to three hours. There was some relief from pain after the first injection and definite relief after three injections. The patient is doing housework and has recently been able to do a complete washing for the first time in two years. Increased motion in the arms is now present. The agglutination titer was raised from 1:0 to 1:6,400 after three injections, and remained at that level after eight injections.

CASE 10—History—In Mrs. A. R., aged 63, pain was present in the right knee for about fifteen years. Stiffness was also present. These symptoms were aggravated by the patient's being on her feet a great deal, the knee was more painful in the evening than in the morning, there was no other joint involvement and no history of any injury. The patient was always of less than average weight. She had a tendency toward constipation and functional gastro-intestinal symptoms.

Examination—General findings were essentially negative. Roentgen examination of the right knee was reported as follows: "There is a definite narrowing of the medial portion of the joint space, such as is commonly associated with a static arthritis. There is a small amount of bone production around the patella and the tibia, characteristic of a chronic hypertrophic arthritis. Opinion: Static arthritis with hypertrophic bone production." A blood culture gave negative result.

Vaccine Therapy—The patient received eight injections of from 100,000,000 to 1,000,000,000 organisms over a period of more than two months. Reactions consisted of slight chills a few hours after injections. On one occasion some diarrhea was present. The knee began to be slightly less painful after the third injection and has continued to improve since that time, so that there is much less pain at the present time and walking is definitely easier. The agglutination titer was raised from 1/200 to 1/12,800 after five injections.

CASE 11—History—Mrs. A. J., aged 29, had had pain in the left hip for the past two months so that walking was painful and difficult. There was some pain in other joints, especially the left knee.

Examination—The patient walked with a definite limp. Pain was present over the hip on abduction of the thigh. Roentgen examination of the left hip and left knee was reported as follows: "There is a very slight hypertrophic change around the left hip, suggesting an old, rather low grade arthritis. A small amount of effusion is present in the left knee. Conclusions: effusion of left knee, slight hypertrophic arthritis of the left hip." A blood culture gave negative results.

Vaccine Therapy—The patient was given ten treatments over a period of three months at intervals of from four to twenty days with doses of from 100,000,000 to 4,000,000,000 organisms. Most of the last doses were from 1,000,000,000 to 2,000,000,000. Slight or no chills and fever occurred after most injections, this reaction was quite marked for seven hours after the dose of 1,000,000,000. The joints were definitely less painful after four injections, and after that time the patient walked without a limp. She stated recently that there is now only occasional joint pain and that she is much improved. Skin tests have remained positive. The agglutination titer was raised from 1/0 to 1/3,200 after seven injections.

CASE 12—History—A. G., aged 57, had had joint pains for years, they began in the knees and elbows and extended to nearly all the joints. He was in the hospital in 1921 for this condition, at which time there was slight limitation of motion in the right shoulder, elbows and wrists. At that time he had all infected teeth removed, and tonsillectomy was done. A roentgenogram of the knees was made at that time (1921) and interpreted as follows: "Moderate hypertrophic changes involving the articular surfaces. Conclusions: hypertrophic arthritis, both knees."

Examination—The patient walked with some difficulty, using a cane. He had limitation of motion of the knees, hips, wrists, elbows and shoulders. Roentgen observations in 1931 were: "There is a considerable loss of the articular cartilage in the right knee joint with some evidence of new bone formation. The appearance is quite characteristic of an infectious arthritis in the stage of repair. Only a slight narrowing of the right ankle joint with considerable atrophy of the bone. The change appears to be chiefly periarticular. Conclusions: infectious arthritis, right knee joint, probable periarticular arthritis, right ankle joint." A blood culture yielded *Streptococcus viridans*.

Vaccine Therapy—Thirteen injections were given over a period of three months at one week intervals. The dose was from 100,000,000 to 2,000,000,000 organisms. Reactions varied from moderate chills and fever for twenty minutes to more severe chills and fever for four or five hours. There has been no definite improvement in joint pain or stiffness. The agglutination titer was raised from 1/200 to 1/12,800 after seven injections.

CASE 13—History—Mrs. C. M., aged 61, had had persistent pain in the region of the thoracic spine for six years (since 1925). Pain often would waken her at night and was present at all times when she was working. She had also had slight pains in the ankles and knees during the past four years. These pains were inconstant and not severe, and were noticed chiefly on damp rainy days.

Examination—Limitation of motion of the thoracic spine was observed. Other joints showed no changes. The roentgen report was, "Thoracic spine. There is a marked scoliosis of the thoracic spine. There is some evidence of atrophy of the bodies. There is only a slight amount of hypertrophic arthritis present." A blood culture showed *Streptococcus viridans*.

Vaccine Therapy—Fourteen injections were given over a period of three months at one week intervals. The dosage was from 100,000,000 to a maximum of 2,000,000,000 organisms, the last eight injections being 2,000,000,000. The patient had no reaction from the first two injections. With the larger dosage she had no reactions at times, but at other times had chills and fever for three or four hours. Herpes labialis was noted on one occasion and increased aching for a few hours on another occasion. She had no relief until after five injections. Since that time, the previous moderate pain in the extremities has subsided, and the severe backache has entirely disappeared for the first time in six years. While previously unable to walk more than two blocks because of severe back pain, she can now walk several miles. Some residual stiffness persists through the thoracic spine, but there is no severe pain. The agglutination titer was raised from 1/0 to 1/200 after two injections.

CASE 14—History—Mrs. T. D., aged 64, had had marked pain and swelling in the knees for the past six months. The pain was worse on motion after a rest period.

Examination—The patient walked with a limp. The knees were definitely tender and swollen. Roentgen observations on the left knee were "There is a slight degree of chronic hypertrophic arthritis, involving the left knee joint and the patella. There is no evidence of destruction of cartilage or of bone. Conclusion: slight chronic hypertrophic arthritis." A blood culture was negative.

Vaccine Therapy—The patient received thirteen treatments over a period of three and one-half months. The dosage varied from 100,000,000 to 5,000,000,000 organisms. The last four doses were reduced to 3,000,000,000. Reactions were variable, none was present until a dose of 1,000,000,000 was used. With a larger dosage she had no reaction at times, and at other times chills and fever of from two to four hours' duration. After the second injection, the pains were much lessened and swelling subsided in the knees. Improvement has continued. Skin tests, strongly positive before treatments, became negative after three injections and remained negative when rechecked after five injections. The agglutination titer was raised from 1/100 to 1/800 after two injections.

CASE 15—History—Mrs. C. V., aged 78, first noticed pain in the knees ten years before this report (1921). The pain became quite severe, and she used crutches for seven years, discarding them three years ago. A roentgenogram taken in 1921 showed a definite hypertrophic arthritis of the right knee. During the

past ten years the patient had never been free from joint pains, especially of the hands. She stated that swollen tender lumps appeared over the phalangeal joints and persisted for several months, leaving hard, painless lumps in their place.

Examination—Some swelling and tenderness were noted over the knees, especially the right. There was some enlargement of many of the phalangeal joints. There were a few tender soft masses over some of the phalangeal joints. One of these was removed, and section showed a small cyst with an inflammatory wall. Roentgen observations on the right knee (1921) were "Definite new bone formation characteristic of hypertrophic arthritis." A report on the left hand (1931) was "There is a distinct loss of cartilage in the interphalangeal joints with some hypertrophic changes. Slight loss of cartilage is present in the wrist joint. The appearance suggests a chronic arthritis of the hypertrophic type mixed with the atrophic type. Conclusions atrophic and hypertrophic arthritis, left hand." A blood culture showed *Streptococcus viridans*.

Vaccine Therapy—The patient received nine injections over a period of two months at one week intervals. The doses varied from 100,000,000 to 400,000,000 organisms. At times no reaction followed, at other times, moderate chills and fever, on one occasion the patient had chills for three hours and fever for four hours. The joints were less painful after the second injection and have continued to be less painful since that time. The patient also walks more easily and with very little limp. Intradermal skin tests, which were positive before treatment, were negative when tested after seven injections. The agglutination titer was raised from 1/400 to 1/25,000 after eight injections.

CASE 16—History—Mr. M. E., aged 71, fell thirty-five years ago and struck the left shoulder. He was able to work immediately afterward. Two years later he developed pain in that shoulder and had had pain constantly since. He was unable to put on his coat without help because of the pain. He had tried many types of medication without relief. No other joints were involved.

Examination—There was limitation of motion in the left arm at the shoulder. Roentgen observations on the left shoulder were "There is a marked chronic hypertrophic change about the acromioclavicular joint, especially involving the acromion process. The appearance suggests most strongly an old injury with secondary changes, but the possibility of hypertrophic arthritis must be strongly considered. Conclusions hypertrophic arthritis or old injury of left acromioclavicular joint." A blood culture showed *Streptococcus viridans*.

Vaccine Therapy—The patient received five injections of from 100,000,000 to 2,000,000,000 with no reactions or relief from pain.

CASE 17—History—Mrs. B. S., aged 57, had had pain and, at times, swelling in many joints for ten or twelve years. The hands had frequently been involved, and there had also been some pain in the knees, ankles and shoulders. During the past two weeks, the soreness had been more marked, especially in the left knee.

Examination—The patient walked with a limp. Some swelling and tenderness were present over the left knee. Roentgen observations on the left knee were "There is a fairly marked hypertrophic arthritis, involving the left knee joint, with a number of spurs projecting from the tibia and patella. Conclusions chronic hypertrophic arthritis." A blood culture yielded *Streptococcus viridans*.

Vaccine Therapy—The patient received nine injections, from 100,000,000 to 2,000,000,000 organisms, over a period of two and one-half months. The reactions varied, the patient usually having chills and fever of about four or five hours' duration, on one occasion she had some fever for a day. The joints were less painful after the second injection, and the swelling in the knees definitely sub-

sided. The patient has markedly improved, she walks easily and with very little pain. Skin tests, previously positive, became negative after five injections. The agglutination titer was raised from 1:100 to 1:12,800 after five injections.

CASE 18—History—Mr. U. G. S., aged 68, had had pain in the knees and in the back for the past seven years (since 1924). There had also been some pain in the shoulders, elbows and feet, though less marked.

Examination—The patient walked with a slight limp. No gross joint deformities were observed. The roentgen report on the lumbosacral region was: "There is a marked degree of chronic hypertrophic arthritis, involving the whole lumbar spine. Conclusion: chronic hypertrophic arthritis." A blood culture showed *Streptococcus viridans*.

Vaccine Therapy—The patient received nine injections of from 100,000,000 to 2,000,000,000 organisms at weekly intervals over a period of two months. Reactions either were absent or consisted of slight chills and fever, the patient was always up and about. No improvement whatever occurred until after five injections, after which time the pain was much less marked and remained so. The patient now has no pain at night and sleeps well. Pain is absent except after hard work as a gardener.

CASE 19—History—Mrs. H. L., aged 75, had had pain through the back for three or four years. There was no pain elsewhere.

Examination—General findings were negative except for moderate hypertension. There was moderate fixation of the spine, with limited movement. A roentgenogram of the spine and lumbosacral region showed "definite new bone formation and lipping, characteristic of hypertrophic arthritis." A blood culture gave negative results.

Vaccine Therapy—Over a period of two and one-half months the patient received nine injections (100,000,000 to 1,000,000,000). Reactions varied from no chills to chills and fever of from three to five hours' duration and, on one occasion, marked herpes labialis. The backache was definitely better after the second injection, and little or no pain has been present since then, though some stiffness and limitation of motion of the spine persist. The agglutination titer was raised from 1:200 to 1:1,600 after six injections.

CASE 20—History—Mrs. J. F., aged 63, first noticed pain in her right hip seven years before this report, and began to limp at that time. She believed that her right leg was getting shorter. She had had some gradual extension of pain into the spine and had become slightly stooped. She stated that her mother had a similar condition with pains in the hip joints.

Examination—There was limitation of motion in the right hip and tenderness over the right hip and lumbar spine. The patient walked with a limp. Kyphosis was present. The roentgen report was, "Thoracic spine, pelvis, femurs, lumbar spine. Plates of the spine showed a marked kyphosis with some hypertrophic change. Several of the vertebrae, most particularly the twelfth thoracic, show a characteristic change typical of Paget's disease, there being some degeneration and some marked increase in the trabeculae and increased density. The same process is present to a lesser degree throughout the rest of the thoracic and the lumbar vertebrae. Plates of the pelvis show a very marked characteristic Paget's disease, involving especially the whole upper half of the right femur and pelvis of this side. On the left the ilium, sacrum, and to some extent the pelvis are involved, but the femur is not involved. The sacrum throughout is fairly well involved. There is excessive calcification and irregular distribution throughout

There is some calcification of the intervertebral discs. Conclusions generalized Paget's disease or osteitis deformans." A blood culture yielded *Streptococcus viridans*.

Vaccine Therapy—The patient received twelve injections of from 100,000,000 to 1,000,000,000 organisms. The usual reactions were slight chills and fever of a few hours' duration. The joints were definitely less painful after the fourth injection and have continued to remain improved. The patient feels stronger and can walk better since receiving the vaccine. The agglutination titer was raised from 1/200 to 1/6,400 after five injections.

REACTIONS

Immediately following an injection, the patients experienced no reaction that might correspond with the so-called anaphylactic reaction which sometimes follows injections of horse serum. Usually about three hours after the injection, there was a general reaction. Occasionally, this would follow within an hour or occur as much as seven or eight hours afterward. This reaction consisted of chills of varying degree and duration, followed by fever. The chills were usually of one or two hours' duration and the fever of two or three hours' duration. The reaction, however, was by no means constant. Sometimes it might be of little consequence and at other times it might be severe and continue for from twelve to fourteen hours. The temperature, when elevated, was usually from 100 to 101 F., although it was as high as 104 F. in a very few instances. Following about 25 per cent of the injections, there was little or no reaction. In a few instances there would be severe aching at the time of the reaction, especially a backache, although this was present in a minority of cases. Nausea, vomiting and diarrhea were sometimes present. Patients occasionally felt tired and weak the following day, but more often they were inclined to feel no ill after-effects, and in many cases, felt much better.

RESULTS OF TREATMENT

The psychologic factor must be strongly considered in determining the results of any therapeutic measure for arthritis. An attempt was made to eliminate this from consideration as much as possible. The majority of patients had had arthritis for years and had tried many types of medication, diathermy and other physical therapeutic measures. Some had had previous treatments with typhoid vaccine with almost unanimous disappointment. The criteria indicative of improvement were (1) decreased pain, (2) definitely increased motility of joints, (3) ability to return to work and (4) statements from the patients that there had been no recent spontaneous period of sudden improvement comparable with that experienced since being on vaccine therapy. From the foregoing criteria it seemed that about 75 per cent of the patients under-

going treatment reported definite improvement. The remaining 25 per cent showed no improvement and, possibly, in a few instances became worse, though probably not worse than would be expected in their clinical course without treatment. The patients who were helped showed a rather definite tendency toward improvement after a given number of injections.

Analysis of the time of beginning clinical improvement is as follows:

1 treatment	5 per cent improved
2 treatments	47.5 per cent improved
3 treatments	70 per cent improved
4 treatments	71.7 per cent improved

After the fourth injection there was little or no further increase in the percentage of patients showing clinical improvement. Some of the patients who were clinically unimproved had as many as from fifteen to twenty injections without benefit. Those who enjoyed clinical improvement in nearly every instance maintained that improvement during the course of therapy. At this time no definite conclusions as to the permanence of this improvement can be drawn. In some instances the improvement has been transitory, while in other instances it has persisted for one to two months after the last injection. There seems to be an individual variation in the duration of improvement after therapy. This improvement apparently can be maintained by repeating the injections at intervals of from seven to fourteen days.

The agglutination titer rose from an average of 1:132 before treatment to an average maximum titer of 1:11,525 after therapy. The highest agglutination titer after therapy in our series was 1:25,000, and this was obtained in several cases.

The intradermal skin tests were also observed in 25 cases before treatment and after five or more injections. The tests were positive before treatment in every instance. After treatment, nine became negative, six were definitely reduced, and ten remained positive as before the vaccine therapy.

COMMENT

One hundred cases of chronic arthritis were studied in respect to classification, etiology and intravenous vaccine treatment. The chief emphasis is placed on the treatment.

It is difficult to classify these 100 cases of chronic arthritis into definite groups by clinical and roentgen findings. There seems to be a gradual gradation in clinical types from the typical rheumatic arthritis to the degenerative type. There are all kinds of borderline and mixed cases, according to the standard classifications in use at the present time.

The frequency of the presence of the streptococci, usually the viridans strains, recovered from the blood of chronic arthritic patients,

would strongly suggest that in most cases chronic arthritis is infectious in character and is generally due to streptococcic infection. The streptococci are frequently recovered from the blood of patients with the various nonspecific forms of arthritis, such as acute rheumatic arthritis, rheumatoid (proliferative, atrophic) arthritis and osteoarthritis (degenerative, hypertrophic arthritis). It appears that the various clinical types of arthritis may be different manifestations in the pathogenesis of chronic arthritis due to streptococci. There seems to be a general variation in the type of response to infection with different age groups, children most frequently manifest clinical rheumatic fever and the older adults more often develop new bone formation.

The results obtained from vaccine treatment are evaluated from two different angles. 1. By intravenous vaccination two conditions seem to be produced in the patient which are conspicuous in protected animals. There is evidence that the patients who are hypersensitive to streptococci tend to become desensitized, as indicated by a positive skin test becoming negative, and regularly there is a marked increase in the concentration of the streptococcic agglutinins in the patients' serums. Desensitization and a marked increase in the agglutinating titer of the serum are the two conspicuous things noted in vaccinated hypersensitive animals, which are protected from the development of further lesions. 2. The second means of estimating the value of intravenous vaccine therapy in chronic arthritis is the fact that about 75 per cent of the patients become clinically improved, as indicated by a relief from pain, an increase in the motility of the joints, ability to go back to work, etc.

The mechanism of protection is not determined. Two factors are suggested: a desensitization as indicated by the change in the skin test and antibody protection as suggested by the increased agglutinating titer.

Protein shock as a possible beneficial factor must be considered. Experiments in animals indicated that the protective phenomenon was not due to nonspecific protein shock. The results from typhoid vaccine in patients with chronic arthritis were much less favorable, and the reaction much more severe, than when a streptococcic vaccine was used. The clinical improvement in the patients vaccinated with streptococci had no apparent correlation to the amount of shock. In many cases the improvement was most marked when shock was absent.

The protective phenomenon, as indicated by previous experiments, does not seem to be type-specific, but it does seem to be species-specific. *Streptococcus hemolyticus* protected against *Streptococcus viridans*. The protection appears not to be due to nonspecific protein shock. Injections of typhoid vaccine did not protect against *Streptococcus viridans*.

No definite conclusions can be drawn as to the permanence of the results from intravenous vaccine therapy in chronic arthritis. It may be of only temporary value and may necessitate frequent injections over a long period of time to maintain the improvement. Further observations over a long period are necessary to determine the value of this method of treating patients for chronic arthritis, but we know of no other therapy that has given similar clinical improvement in as high a percentage of cases.

CONCLUSIONS

1 The types of arthritis in our series do not fit accurately into any classification now in use. There seem to be many mixed types and a gradation in the clinical picture from rheumatic fever to osteoarthritis (degenerative, hypertrophic).

2 The frequent occurrence of streptococci in the blood stream of patients with various clinical forms of chronic arthritis strongly suggests an etiologic relationship.

3 Intravenous streptococcic vaccination brings about in patients two conditions (desensitization and a high agglutinating titer) that are regularly associated with the protection experimentally developed in animals against streptococci by intravenous vaccination. This analogous condition in vaccinated patients and animals affords a basis for intravenous vaccination in patients having chronic arthritis.

4 Since subcutaneous injections of streptococci in animals tend to increase hypersensitiveness and only produce a low agglutinating titer in the serum, the subcutaneous method of vaccination in chronic arthritis would seem to be of less value than the intravenous method, if not contraindicated.

5 No ill effects have resulted from the intravenous vaccinations in the 100 cases studied. On the other hand, in 75 per cent of the cases the clinical improvement appears to be sufficient to justify the further use of this method of treatment for chronic arthritis.

THIOCYANATE THERAPY IN HYPERTENSION

I OBSERVATIONS ON ITS TOXIC EFFECTS *

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Since Pauli's¹ observation in 1903 that thiocyanate is effective in reducing high blood pressure, the use of this drug has apparently gained favor. Frequent confirmation of this observation, particularly in recent years, seems to have caused rather general acceptance of thiocyanate therapy as offering, in a selected group of persons with hypertension, a method of meeting a difficult therapeutic problem. Ever since Claude Bernard's² first pharmacologic investigation, in 1857, there have been many references to the toxic properties of thiocyanate, but in examining the literature it is noteworthy that, with a few exceptions, mainly its hypotensive property is stressed. The appearance of toxic manifestations thirteen times in a series of seventy-four trials in fifty patients under investigation by us seemed of sufficient importance to report. In two of these thirteen patients there was a fatal outcome. We believe that this is the first report of death in man from thiocyanate administered for therapeutic purposes.

Westphal and Blum³ administered 0.5 Gm three times a day for eight to twelve days in nine patients and noted a tendency to respiratory inflammations, muscle weakness and psychosis. They reported no deaths. Takacs⁴ reported a papular dermatitis following the administration of 1 Gm daily for nine days. Weiss and Ruedemann⁵ and

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2 Bernard, Claude. *Leçons sur les effets des substances toxiques et médicamenteuses*, Paris, J. B. Baillière et fils, 1857, p. 354.

3 Westphal, K., and Blum, R. Rhodan Treatment of Genuine Arterial High Pressure and the Theoretical Foundation for It, *Deutsches Arch f klin Med* **152** 331, 1926.

4 Takacs, I. Versuche mit Rhodansalzen. 1 Einfluss der Rhodan auf Magensekretion, weisse Blutkörperchen, Pulsschläge und Blutdruck, *Ztschr f d ges exper Med* **50** 432, 1926.

5 Weiss, C. R., and Ruedemann, R. Exfoliative Dermatitis from Potassium Sulphocyanate Therapy, *J A M A* **93** 988 (Sept 28) 1929.

Ayman⁶ had a similar experience. A complete summary of the known facts concerning the pharmacologic properties of thiocyanate was presented by Nichols.⁷ His observations on the toxic effects of the drug in guinea-pigs closely paralleled the clinical manifestations in two fatal cases in man observed by us. He collected the reports of four fatalities in man from the literature, in which thiocyanate was taken accidentally or with suicidal intent. The fourth case that he quoted⁸ presented a clinical syndrome practically identical with manifestations noted in our fatal cases. He recommended as a safe dose in man 1 Gm daily. Nerking,⁹ on the other hand, noted toxic effects with doses of from 0.5 to 1 Gm daily. Gager,¹⁰ in a series of thirty-five patients, noted dermatitis in two instances and weakness in one other as the only toxic manifestations. The dosage used was 0.3 Gm daily for one week, 0.2 Gm daily for one week and 0.1 Gm daily for one week. Thereafter 0.1 Gm was given daily or every other day except in obstinate cases, in which 0.3 Gm was given for several weeks. Fineberg¹¹ treated twenty-one patients with 1 Gm of thiocyanate daily for three months and noted no toxic effects. Palmer, Silver and White,¹² using the dosage described by Gager, noted a few instances of weakness and cardiac pain. In a group of twenty-four patients studied by Borg,¹³ unpleasant symptoms developed in thirteen. Toxic psychosis developed in four. There were disorientation, hallucination of sight and hearing, mania, confusion and delusions of persecution. These four patients had received larger doses than the rest. Recovery occurred in all, in from five to seven days after the drug was discontinued. The dosage used in his study was from 0.13 to 0.65 Gm three times daily for from one to four weeks.

This review of the literature is sufficient to indicate, first, that the toxic effects of thiocyanate in man are known and have been repeatedly observed by independent investigators, and second, that while a given dose proves harmless and perhaps therapeutically effective in the hands

6 Ayman, D. Exfoliative Dermatitis from Potassium Thiocyanate, Correspondence, *J A M A* **93** 1671 (Nov 23) 1929.

7 Nichols, J. B. Pharmacologic and Therapeutic Properties of the Sulphocyanates, *Am J M Sc* **170** 735 (Nov) 1925.

8 Vintilescu, J., and Popesco, A. *Ann d'hyg* **25** 239, 1916.

9 Nerking, J. Toxic Action of Thiocyanates, *Deutsche med Wchnschr* **39** 945, 1913.

10 Gager, L. T. The Incidence and Management of Hypertension, with a Note on Sulphocyanate Therapy, *J A M A* **90** 82 (Jan 14) 1928.

11 Fineberg, M. H. Potassium Thiocyanate in Treatment of Patients with Hypertension, *J A M A* **94** 1822 (June 7) 1930.

12 Palmer, R. S., Silver, L. S., and White, P. D. The Clinical Use of Potassium Sulphocyanate in Hypertension, *New England J Med* **201** 709 (Oct 10) 1929.

13 Borg, J. F. Use of Sulphocyanates in Treatment of Hypertension, *Minnesota Med* **13** 281 (May) 1930.

of one investigator, it produces severe and often dangerous manifestations in the hands of another.

Two groups of patients were studied. One group was given ambulatory treatment in the outpatient department and the other group was observed while confined to bed in the hospital. The hospital group, for the most part, received its medication from one person. In the ambulatory group, only those patients were selected for study by whom, we felt, it was reasonably certain that the thiocyanate was being regularly taken as prescribed. Patients treated in the hospital were observed once or more often each day. The ambulatory patients were, in most instances, observed weekly. Both sodium and potassium salts of thiocyanate were used indiscriminately, and no record was kept of the pa-

TABLE 1—*Summary of Data on Thirteen Patients with Essential Hypertension Who Showed Toxic Effects After Thiocyanate Administration*

Case	Group	Total Dose at Time of Thiocyanate Intoxication, Gm	Residual Drug at Time of Thiocyanate Intoxication, Gm	Average Daily Dose, Gm	Duration of Medication, Days	Fall in Blood Pressure at Time of Thiocyanate Intoxication
1	Hospital	8.15	5.73	0.815	10	No
2	Hospital	11.34		1.62	7	No
3	Hospital	32.54		0.638	51	Yes
4	Hospital	14.49		0.805	18	Yes
5	Hospital	12.71	5.00	0.978	13	No
6	Hospital	5.87	5.22	0.652	9	No
7	Hospital	26.62	21.56	1.21	22	Yes
8	Hospital	9.78	8.49	0.652	15	No
9	Hospital	14.01		0.326	43	Yes
10	Ambulatory	9.13		0.326	28	Yes
11	Ambulatory	11.34		0.405	28	No
12	Ambulatory	17.11		0.489	35	No
13	Ambulatory	11.73		0.17	69	No

ticular salt used in individual patients. The hypotensive effect of thiocyanate in this series of seventy-four trials is reported in another paper. This study is particularly concerned with the toxic effects of the drug during its administration for therapeutic purposes.

Table 1 represents a summary of the clinical observations in our thirteen patients who showed toxic manifestations. The ages ranged from 29 to 65, and there were eight women and five men. In all patients the hypertension was of the essential type. The average daily dose ranged from 0.17 to 1.62 Gm. The total dosage at the time of thiocyanate intoxication varied from 5.87 to 32.54 Gm. The smallest total dose given was 0.652 Gm daily for nine days, and the largest 0.638 Gm daily for fifty-one days. A distinct and satisfactory fall in blood pressure occurred in five of the thirteen patients. The first nine patients noted in table 1 were observed in the hospital, the last four

were ambulatory. There is noted the amount of residual thiocyanate in the body at the onset of toxic symptoms. The figure for the residual thiocyanate was arrived at by subtracting the total amount of drug excreted from the total amount administered. The quantitative determination of excretion was made on the daily twenty-four hour urine output. The procedure was to acidify 10 cc of the urine and develop a reddish-brown to a cherry-red color with ferric chloride. The unknown was then read against a known standard in a colorimeter. While this method does admit of some inaccuracy, it is clear from table 2 that it is entirely satisfactory for supplying the information that we desired.

TABLE 2—*Recovery of Thiocyanate in the Urine*

Diagnosis	Total Dose, Gm	Total Thiocyanate Recovered		Recovered, per Cent
		Gm	Days	
Chronic diffuse glomerulonephritis	10.37	7.699	30	74
Chronic diffuse glomerulonephritis	1.143	0.939	22	82
Essential hypertension	8.101	7.256	35	89.5
Normal	1.143	1.046	14	91
Normal	36.616	39.831	75	108
Normal	0.652	0.596	10	91
Normal	0.162	0.142	4	88
Normal	5.346	5.709	16	106
Normal	0.326	0.316	9	97

TABLE 3—*Comparison of Two Methods for the Quantitative Estimation of Thiocyanate in the Urine in Man*

Ferric Chloride Method, Gm per 100 Cc	Schreiber's ¹⁴ Method, Gm per 100 Cc	Exact Amount Known to be Present, Gm per 100 Cc
0.0160	0.0165	0.0163
0.0080	0.0100	0.0081

It will be seen that in eight of nine trials, over 80 per cent of thiocyanate was recovered in the urine, and in five of nine trials over 90 per cent was recovered. Furthermore, a correlation of this method with the more involved method described by Schreiber ¹⁴ showed them to be strictly comparable (table 3). That thiocyanate can be quantitatively recovered in the urine was shown by Pollak, ¹⁵ who used an exact titration method.

Because of the difference in the excretion rate of thiocyanate in different individuals, it occurred to us that the total amount of drug taken up to the fall in blood pressure or the onset of thiocyanate

¹⁴ Schreiber, H. Thiocyanate Content of Human Blood Serum, *Biochem Ztschr* **163** 241, 1925.

¹⁵ Pollak, L. Ueber das Schicksal der Rhodanate im tierischen Organismus. *Beitr z chem Physiol u Path* **2** 430, 1902.

intoxication did not give a true account of the actual amount necessary to produce these effects. It therefore seemed necessary to make accurate and daily observations on the amount of thiocyanate taken and the amount excreted, to determine the amount of residual drug in the body at the first evidence of its effect. Accordingly, a group was selected consisting of three persons with normal blood pressure, six with essential hypertension and two with hypertension associated with chronic diffuse glomerulonephritis. The results of these observations are shown in table 4. There can be little doubt from the observations presented that toxic effects and even a fatal outcome may occur in some patients who have in their tissues a smaller amount of thiocyanate than others who not only do not become toxic but experience a satisfactory fall in

TABLE 4—*Amount of Thiocyanate in the Body at the Time of the First Definite Fall in Blood Pressure and at the Time of the First Sign of Intoxication*

	Dosage, Gm		Residual Drug at First Fall in Blood Pressure, Gm	Residual Drug at Intoxication, Gm	Average Daily Thiocyanate Output in Urine, Gm
	Total	Average Daily			
Nephritic*	9.78	0.978	8.96		0.097
Nephritic*	10.80	1.080	9.03		0.275
Essential hypertension	9.78	0.652		8.49 (died)	0.086
Essential hypertension	12.71	0.978		5.00	0.536
Essential hypertension	8.15	0.815		5.73	0.213
Essential hypertension	9.78	0.978	8.09		0.192
Essential hypertension	5.87	0.652		3.22	0.151
Essential hypertension	26.62	1.210	20.88†	21.56	0.262
Normal	4.89	0.978	2.29		0.339
Normal	4.56	0.326	2.89		
Normal	3.26	0.652	2.90		0.115

* Associated with diffuse glomerulonephritis

† See text

blood pressure. There is only one exception to this observation, in the one patient who exhibited signs of intoxication after the enormous amount of 21.56 Gm. of thiocyanate had accumulated in the body. It is interesting that in this patient there occurred a satisfactory fall in blood pressure seven days after the drug was discontinued and after 0.68 Gm. had been excreted. It apparently required a smaller amount of residual thiocyanate to effect a fall in normal blood pressure than when the pressure was abnormally elevated.

Of the fifty patients with hypertension in this series treated seventy-four different times with thiocyanate, thirteen presented toxic manifestations. In eleven of these the toxic manifestations disappeared within a few hours to four days after discontinuance of the drug. The usual order in which the toxic symptoms made their appearance was as follows: muscular fatigue accompanied or followed by nausea, vomiting

disorientation and mental confusion, motor aphasia, hallucinations of sight and hearing, and, in the fatal cases, progression to delirium, convulsive twitchings, coma and death. The frequency with which these toxic manifestations were observed is shown in table 5. It is noteworthy that while ambulatory patients who become toxic notice muscle fatigue as the first indication, this symptom may pass entirely unnoticed in patients confined to bed. In these bed patients it is not unusual for motor aphasia, mental confusion or even hallucinations to be the first sign of thiocyanate intoxication.

The remaining two patients who became toxic finally died of thiocyanate poisoning in spite of drastic measures to induce elimination of the drug.

The first fatal case was that of patient M, aged 40. Her hypertension was of the essential type. The duration of her hypertension was not known. Three months before admission to the hospital she

TABLE 5—*Frequency of Occurrence of Toxic Manifestations*

Toxic Manifestations	Frequency of Occurrence
Nausea	8
Muscular fatigue	7
Vomiting	7
Mental confusion and disorientation	7
Hallucinations of sight and hearing	6
Motor aphasia	3
Death	2
Dermatitis	1

developed a severe occipital headache, which was continuous, and dimness of vision. Her blood pressure during the control period, ranged between 255 systolic and 130 diastolic and 204 systolic and 100 diastolic. The fundi showed the classic changes of malignant hypertensive neuroretinitis. The concentration test showed a fixation of specific gravity between 1.008 and 1.014. The red blood cells numbered 4,000,000, and the hemoglobin content was 50 per cent. The urine was negative for albumin and blood. On the thirteenth day after admission thiocyanate was begun in dosage of 0.652 Gm. daily. On the fourteenth day, after 9.12 Gm. had been given, the patient complained of nausea and the blood pressure was 186 systolic and 96 diastolic. On the following day nausea was more marked, but the blood pressure had risen to 220 systolic and 110 diastolic, so that another dose of 0.652 Gm. was given. Later on this day she became somewhat confused and incoherent. Thiocyanate was discontinued. A total of 9.77 Gm. had been given in fifteen days. The blood pressure continued high, and on the following day she became violently delirious with hallucinations of sight and hearing, extreme motor restlessness, nystagmus and frequent convulsive movements of

the extremities. She was completely disorientated, continually muttering and thrashing about so violently as to require mechanical restraint. During the last twenty-four hours she voided almost no urine and was markedly dehydrated in spite of repeated saline hypodermoclyses and dextrose infusions. The stuporous state became more profound, and death occurred sixty-six hours after thiocyanate had been discontinued. On the day of death, the blood pressure was 212 systolic and 106 diastolic. Seven days before the end the nonprotein nitrogen content of the blood was 33 mg per hundred cubic centimeters. Two days before the end the nonprotein nitrogen content was still within the normal range, being 45 mg, and the creatinine 2.4 mg per hundred cubic centimeters. On the same day the urea clearance showed 41.2 per cent of normal function for the first hour and 34.8 per cent for the second hour. At the time of onset of the toxic symptoms, 1.29 Gm of thiocyanate

TABLE 6—*Analysis of Tissues for Thiocyanate Content*

Tissue	Estimation of Thiocyanate Content of Tissues of a Patient in Whom the Drug Proved Fatal,*	Estimation of Thiocyanate Content of Tissues of a Patient to Whom no Thiocyanate Was Given,
	Mg per 100 Gm	Mg per 100 Gm
Heart	9.7	
Kidney	15.4	Trace
Spleen	9.2	Trace
Liver	14.5	4.0
Lung	17.0	None
Bone	None	None
Brain	8.0	None

* Patient M (see text)

had been recovered in the urine, leaving a residual of 8.49 Gm. A necropsy was performed. The anatomic findings were: lungs, congestion, heart, pericardial effusion, hypertrophy, inactive mitral stenosis and subendocardial hemorrhages, atheroma and ulceration in the abdominal aorta, kidneys, nephrosclerosis with profound arteriolar sclerosis, but no necrotizing lesions, and predominantly normal glomeruli, brain, edema.

The fresh tissues were analyzed for thiocyanate content. Table 6 indicates the results of the analysis as compared with the tissue content in a patient who had not received the drug during life. These analyses were made by Dr. Kenneth Blanchard of the department of biology, New York University. The method used was as follows. The tissues were carefully washed free from blood. Ten gram portions of each tissue were weighed out, frozen with carbon dioxide snow and triturated with 25 cc of water. This mixture was centrifugated and the residue washed. To the washed residue was added 50 cc of water. To 15 cc of the extract was added 15 cc of trichloroacetic acid, this was allowed

to stand for fifteen minutes and filtered To 10 cc of the filtrate was added 7.5 cc of Schreiber's¹⁴ reagent, and the color so developed was read against a standard thiocyanate made with 5 per cent trichloroacetic acid

The second fatal case was that of patient Mic, a woman, aged 56 Her hypertension was of the essential type During the control period her blood pressure ranged from 220 systolic and 130 diastolic to 190 systolic and 100 diastolic After receiving a total of 14.49 Gm in eighteen days, an average daily dose of 0.805 Gm, she complained of nausea The thiocyanate was immediately discontinued There had been no appreciable fall in blood pressure Forty-eight hours after the drug had been discontinued she developed nervous manifestations almost identical with those described in patient M In spite of all measures to induce elimination she persisted in this state for six days and died Two days after thiocyanate was stopped, the blood pressure fell to 158 systolic and 90 diastolic, and on the day of death, four days later, it was 90 systolic and 30 diastolic Necropsy was not permitted

COMMENT

Nichols⁷ administered lethal doses of thiocyanate to guinea-pigs and noted a characteristic train of signs and symptoms In the final state of poisoning he noted intense stimulation and irritation of the motor cells of the spinal cord, extreme muscular weakness, tremors and finally generalized tonic and clonic convulsions, rigidity, coma and death Our two fatal cases in man presented manifestations entirely comparable to those described in guinea-pigs

In an attempt to explain the occurrence of toxic phenomena, one is first concerned with the dosage used It might be expected that toxic manifestations would occur only when the larger dosages were given That this is not so in the case of thiocyanate is clear from table 4 Severe toxic manifestations occurred in some patients who had received less of the drug, both in total and average daily dosage, than others who developed no toxic signs This confirms an observation by Nichols,⁷ who found that some guinea-pigs succumbed to 200 mg per kilogram of body weight, while others survived 300 mg

Our data lead us to believe that some persons, for reasons which are not clear, show a distinct susceptibility to thiocyanate This susceptibility manifests itself by certain symptoms of which the earliest are muscular weakness and nausea It further appears from our observations that in certain persons there is little or no margin of safety between the toxic and therapeutically effective dosage of thiocyanate At this time we know of no way of distinguishing those persons who will exhibit susceptibility from those in whom the drug lowers blood pressure effectively without the development of toxic symptoms

SUMMARY

Data are presented on thirteen patients who showed toxic manifestations from thiocyanate, administered for therapeutic purposes

Two of these patients died as a result of thiocyanate poisoning

The incidence of toxic manifestations in this series was 17 per cent

The frequency and order of appearance of the various toxic manifestations are noted

A fall in blood pressure, the occurrence of toxic manifestations and death were found to be unrelated to the amount of thiocyanate administered or to the amount of residual drug in the body

Data are presented showing that in some patients there is little or no margin of safety between the toxic and therapeutically effective dose of thiocyanate

Tissue analysis for thiocyanate and necropsy observations are presented in one of the fatal cases

THE EFFECT OF INSULIN THERAPY ON PANCREATIC ENZYMES IN MALNUTRITION *

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The present study was undertaken to discover whether insulin therapy, when applied to nondiabetic patients with malnutrition promotes the normal secretion of pancreatic enzymes and to prove thereby that the striking gains in weight in such a group may be attributed in part to an increased digestion and assimilation of aliment. Other investigators¹ have shown that the ingestion of the same diet without insulin produced comparatively slight increase in weight. In the recent literature on carbohydrate metabolism,² physiologists accept the fact that the hypoglycemia produced by the injection of insulin, and acting on the secretory and motor centers in the medulla, causes gastric and intestinal hypermotility, as well as pancreatic and biliary hypersecretion. The effect of the injection of insulin in augmenting the normal function of the tissues to hold water, carbohydrate, fat and protein is the fundamental criterion of insulin therapy and will be mentioned later in the discussion on the action of insulin. In this study the potency of the pancreatic enzymes was quantitatively measured before and after four weeks' administration of insulin. The results obtained in a group of twenty asthenic, or undernourished, nondiabetic patients, all of whom sought relief for gastro-intestinal disease or symptoms, tend to show that after the course of insulin the pancreatic enzymes exhibited uniformly an increased potency. The presence of bile rich in salts and a normal duodenal mucosa are of course essential to the normal activity of the pancreatic enzymes.

* Submitted for publication, July 28, 1931

¹ From the Gastro-Intestinal Clinic, Out-Patient Department, Pennsylvania Hospital

² Read before the Thirty-Fourth Annual Meeting of the American Gastro-Enterological Association, Atlantic City, May 5, 1931

1 Appel, K E, Farr, C B, and Marshall, H K. Insulin in Undernutrition in the Psychoses, *Arch Neurol & Psychiat* **21** 149 (Jan) 1929

2 Okada, S, Kuramochi, K, Tsukahara, T, and Ooinoue, T. The Humoro-neural Regulations of the Gastric, Pancreatic and Biliary Secretions, *Arch Int Med* **43** 469 (April) 1929. Carlson, A J. The Extrinsic Nervous Control of the Large Bowel, *J A M A* **94** 78 (Jan 11) 1930

Twenty patients were selected and volunteered for the study. Two were not included in the survey, a test for sugar tolerance proved one patient to be a prediabetic, and the other to be hypoglycemic. The remaining eighteen were suffering from gastro-intestinal diseases or symptoms, the latter associated with other systemic diseases. The following diagnoses were made: achylia gastrica, four, pernicious anemia, three, gastroduodenal new growth, three, chronic eczema, two, giardiasis, two, visceroptosis, two, hyperthyroidism, one, and senility, one.

METHODS

The pancreatic enzymes were estimated twice prior to the four weeks' course of insulin and once or twice thereafter. The three fractions: duodenal residue (*A*), after stimulation (*B*), and later flow (*C*) were separately studied for amylase, trypsin and lipase so that as many as twelve measurements of potency of each enzyme were recorded for the same patient. The stool was examined before and after the administration of insulin to compare the degree of digestion of food elements. Estimations of blood sugar in order to insure normal or decreased curves for sugar tolerance, basal metabolism readings and Sellards' bicarbonate test of urine excreted during fasting were included in the survey.

Amylase was studied quantitatively by the Gaultier method, as modified by Lueders, Bergeim and Reh fuss,³ trypsin and lipase were estimated as to their concentration, expressed in minutes and fractions thereof, the aforementioned methods being used, with a further most essential modification of Hollander,⁴ who applied the "time law" of Hedin⁵ for trypsin and lipase. "To obtain the same effect with varying amounts of an enzyme, the time of digestion must vary inversely with the concentration of enzyme." This law does not apply to amylase activity, in which the factor of reversibility is negligible and in which a direct linear proportionality exists between the amount of enzyme present and the amount of hydrolysis effected.

The aforementioned methods show only a narrow range for normal concentration of the three enzymes, and have restored a faith in the clinical value of routine pancreatic ferment studies, which all previous methods, including our own, had well nigh destroyed. The monograph, "The Nature of Enzyme Action" by Sir William M. Bayliss,⁵ published in 1925, is invaluable to the student of general cellular metabolism as effected by enzymic power of decomposition and assimilation.

ADMINISTRATION OF INSULIN

I was fortunate in having the cooperation and assistance of the diabetes clinic of the Pennsylvania Hospital. It was there that the clinic

3 Lueders, C. W., Bergeim, O., and Reh fuss, M. E. Quantitative Determination of Enzyme Activity in Duodenal Fluids, *Am. J. M. Sc.* **166** 535 (Oct.) 1923.

4 Hollander, E., and Marcus, J. M. Pancreatic Function. I. The Quantitative Determination of Pancreatic Enzymes, *Arch. Int. Med.* **36** 585 (Oct.) 1925.
Hollander, E. A Clinical Method for the Quantitative Determination of Pancreatic Ferments in Duodenal Contents, *J. Lab. & Clin. Med.* **16** 460 (Feb.) 1931.

5 Bayliss, Sir W. M. The Nature of Enzyme Action, London, 1925.

patients were taught the use of the syringe and insulin and given a typewritten form of a schedule of administration of insulin and of a diet rich in carbohydrates and fats. This schedule followed closely that of Appel, Farr and Marshall,¹ except that to the ambulatory patients no injections were given in the middle of the day. Twenty units given twice daily was the average maximum dose for both sexes. Hypoglycemic reactions were more frequent in the women; visual symptoms, sweating and especially weakness, which disappeared within half an hour after the ingestion of sweetened orange juice, a chocolate bar or other food. The average cost for the four weeks' insulin study did not exceed \$5 per patient. The insulin was purchased at hospital cost, the syringes (Lilly "Unit" graduated) were loaned on the payment of a deposit.

TABLE 1—Units of Insulin Administered During Experiment

Days	Breakfast Units	Dinner Units
1	5	5
2	5	5
3 to 6th	10	10
7 to 13th	15	15
14 to 20th	20	20
21 to 27th	20	25
28 to 34th	25	30
34 to 40th	30	30

Note.—Since the body appears to become more or less insulin resistant after the tenth day and the appetite less keen after insulin, it is advisable to step up the early doses by five units, if symptoms of hypoglycemia are relieved by frequent feedings. The greater the appetite the first ten days the more rapid the gain in weight.

SCHEDULE FOR THE ADMINISTRATION OF INSULIN

To be given from fifteen to thirty minutes before breakfast and dinner, in fleshy outer portions of arm and thighs, in rotation to prevent local inflammation; small raised itching nodules relieved by alcohol dressings.

Principles of Diet with Insulin 1 High carbohydrate and fat diet 2 Sugar to relieve symptoms of hypoglycemia 3 Diet of 4,000 calories causes rapid gain. 4 Carbohydrate needs 30 Gm per ten units of insulin 5 Fat meats aid in rapid gain, lean meats increase musculature throughout body.

Average full diet: farina, vegetable soup, potatoes, biscuits, oranges, oatmeal, cream, butter, eggs, toast and bread with excess butter. Add vitamin "B" rich foods, whole grain cereals, asparagus, tomatoes, beans, leafy vegetables, milk, spinach, bananas, yeast. Give extra large meat helping and extra helping of vegetables.

Give 1 A vitamin B concentrate (Bemax), tablespoonful in orange juice or on cereal at breakfast. One glass of milk containing two teaspoonfuls of malted milk, two eggs, 1 ounce of cream and one teaspoonful of sugar mid-morning and mid-afternoon.

2 Two pieces of buttered toast and one glass of milk at bedtime.

- 3 Patient never to be without lump sugar or chocolate bar to take if symptoms of hypoglycemia occur
- 4 Weigh patient once weekly, preferably nude
- Note 5 Symptoms of hypoglycemia If patient becomes weak, restless, pale, perspires, trembles, has rapid pulse, shortness of breath, vertigo or visual changes, give sugar, chocolate bar or the juice of two oranges and a teaspoonful of dextrose and call a physician
- 6 To hospital patients with insulin shock from large doses, give 25 or 50 Gm of dextrose intravenously
- 7 At the most active part of the day, more food must be eaten to counteract the endogenous insulin formed

QUANTITATIVE ESTIMATION OF ENZYME ACTIVITY

Collection of Samples—Follow the regular Lyon technic for duodenal drainage with the following departures

- 1 After extracting the gastric contents with a syringe, do not give gastric lavage
- 2 Never use the syringe for the collection of duodenal samples, use only gravity return
- 3 Keep the upper end of the duodenal tube open throughout the twenty minute gradual passage of the tip from the 50 cm mark to 1 inch (2.5 cm) beyond the 70 cm mark
- 4 If possible, avoid stimulation with 100 cc of hot water either to locate the tip or to relax the sphincter oddi, until after another twenty minutes. When the forefinger is placed as a support under the tube and the finger is slid away from the patient's lips, a good tug on the tube usually denotes that the tip is in the duodenum. If there is no duodenal residue, give 50 cc of hot water and allow an immediate return, which usually effects a common duct bile (A) return
- 5 Give a half stimulation, 37.5 cc of a 33 per cent solution of magnesium sulphate. Wait five minutes before permitting siphonage
- 6 Discard all samples that are cloudy or opaque (gastric juice), or that contain free hydrochloric acid or a total acidity of over 0.2 cc of tenth-normal hydrochloric acid for 1 cc of sample
- 7 If the returns are cloudy, place the patient on his back until samples begin to flow clear
- 8 After 10 cc of "B" and "C" bile is collected, the drainage is completed, and the Lyon technic is resumed, with duodenal instillation of physiologic solution of sodium chloride and giving of nutriment before the patient leaves the office or clinic
- 9 Collect all samples in small tubes or flasks surrounded by cracked ice in small beakers or enamel bowls. Samples of 10 cc (crystal clear) are sufficient
- 10 Place samples immediately in ice chest if enzymes cannot be estimated at once, which is the ideal method

Amylolytic Activity—Amylase is determined⁴ by estimating the maltose formed by the action of 1 cc of duodenal fluid on 20 cc of a 5 per cent solution of starch made neutral or faintly pink, with phenolphthalein as indicator (Merck's soluble starch according to Lintner was used). Since amylase is most active on the acid side of neutrality, the slight acidity of the duodenal fluid (from 0.1 to 0.2 cc tenth-

TABLE 2—Laboratory Data Before and After the Administration of Insulin

Sellards' Test after Insulin															Before Insulin															After Insulin																																																																																																																																																																				
No	Name	Diagnosis	Sugar Tolerance			Rate of Sodium Bicarbonate Metabolism	Sellards' Test,* Blood Insulin, Sodium Bicar- bonate, Min			S	Stool	Weight	Vegetative cells, dry, fair diges- tion	Tryp sin, Min	Lipase, tose, Min Gm	Amy- lase Mal Gm	Stool	Tryp sin, Min	Lipase, tose, Min Gm	Amy- lase Mal Gm	Stool	Tryp sin, Min	Lipase, tose, Min Gm	Amy- lase Mal Gm																																																																																																																																																																										
			1 Hr	2 Hr	3 Hr		1	H D S	Chronic eczema																91	141	120	96	—5	10	5	82	104	Vegetative cells, dry, fair diges- tion	10	+15	0.77	112½	Vegetative cells, moist, good digestion	1½	3½	1.20	3½	5½	0.60	2	O B	Achylia, glossitis, optic atrophy	90	270	225			10	5	82	104	Striated and unstriated muscle, scybals	6	7	0.70	80¾	Molst, rare striated muscle	2½	2½	0.60	3	D H II	Achylia, chronic malaria	95	102	106	119		10	5	124½		Occasional fat, occasional muscle	5	4½	0.50	1.1	No fat, occasional muscle	1¾	3¾	0.60	4	P M	Achylia	95	195	113					122¾		Good digestion	2	2	0.62	130	Good digestion	2½	3¼	0.60	5	C I	Permeious anemia	145	225	225			15	10	151¼		Not examined	2½	½	0.42	161¼	Occasional fat, occasional muscle	2	2½	0.63	6	I I O	Chronic eczema, anæmiæ	135	250	160			5	5	154½		Scybals, few meat fibers	3	12	0.46	167½	Moist, occasional striated muscle	1	4	0.60	7	S R	Achylia, gastric tumor	82	134	90					123		Occasional meat fiber, dry	2	7¾	0.82	128½	Occasional starch, moist	3½	1½	0.37	8	T G	Achylia, gastric tumor	112	221	234	126		10	5	93		Excess fat, occasional meat fiber, diarrhea	4½	+20	0.33	110	No fat, meat or starch formed	6	5¼	0.30	9	M MeG
1	H D S	Chronic eczema	91	141	120	96	—5	10	5	82	104	Vegetative cells, dry, fair diges- tion	10	+15	0.77	112½	Vegetative cells, moist, good digestion	1½	3½	1.20	3½	5½	0.60																																																																																																																																																																											
2	O B	Achylia, glossitis, optic atrophy	90	270	225			10	5	82	104	Striated and unstriated muscle, scybals	6	7	0.70	80¾	Molst, rare striated muscle	2½	2½	0.60																																																																																																																																																																														
3	D H II	Achylia, chronic malaria	95	102	106	119		10	5	124½		Occasional fat, occasional muscle	5	4½	0.50	1.1	No fat, occasional muscle	1¾	3¾	0.60																																																																																																																																																																														
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6	I I O	Chronic eczema, anæmiæ	135	250	160			5	5	154½		Scybals, few meat fibers	3	12	0.46	167½	Moist, occasional striated muscle	1	4	0.60																																																																																																																																																																														
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8	T G	Achylia, gastric tumor	112	221	234	126		10	5	93		Excess fat, occasional meat fiber, diarrhea	4½	+20	0.33	110	No fat, meat or starch formed	6	5¼	0.30																																																																																																																																																																														
9	M MeG	Scurvy (1 week of insulin)	90	187	203	183	—10			141½		Soft, fair digestion of starch and fat	3	+20	0.21	143½	Diarrhea, fair digestion	2¾	5½	0.27																																																																																																																																																																														

normal) is sufficient to effect this condition of the substrate with loss of pink color. Incubate flasks for one hour at 37 C, shaking them every fifteen minutes. When the flasks are removed, add a small amount of sodium carbonate to stop digestion. Pour the digestion mixture into a 10 cc buret and run slowly, then drop by drop into 5 cc of boiling Benedict's quantitative reagent, to which has been added from 1 to 2 Gm of sodium carbonate and a small amount of powdered talc (to prevent bubbling over). When the last blue color disappears but before the gray changes to decided pink, the end point is reached. The buret reading, divided into 0.0149 (the number of grams of maltose required to reduce 5 cc of Benedict's reagent) gives the amount of maltose in 1 cc of the digestion mixture. This figure is multiplied by 20 to obtain the total amount of maltose formed (table 2a).

Tryptic Activity—For a transparent water bath, use a 2 to 4 liter pyrex beaker, fill three-fourths full of warm water, set on a high tripod above a micro-burner and maintain a temperature of from 37 to 40 C. Insert a circular copper test tube rack with holes to support six or more large test tubes with a capacity of about 50 cc, and a diameter of 1 inch. Mark three tubes trypsin *A*, trypsin *B* and trypsin *C*. Pipet into each tube 25 cc of a neutral 5 per cent emulsion of melted gelatin. Test

TABLE 2a—*Conversion for Total Maltose*

Buret Reading, Cc	Maltose, Gm	Buret Reading, Cc	Maltose, Gm
0.3	0.99	1.1	0.27
0.4	0.74	1.2	0.25
0.5	0.60	1.3	0.23
0.6	0.50	1.4	0.21
0.7	0.42	1.5	0.20
0.8	0.37	1.6	0.19
0.9	0.33	1.7	0.17
1.0	0.30	1.8	0.16
		2.0	0.15

samples of duodenal fluid for acidity. Discard samples containing free hydrochloric acid or having a total acidity of over 0.2 cc tenth-normal for 1 cc of duodenal fluid. For correction add the identical amount of tenth-normal sodium hydrochloride to the neutral substrate in the proper test tube. Start a time clock (such as the Interval Timer of the Victor Electric Corporation). Record time in minutes and fractions as 0.5 cc of each duodenal extraction is delivered from a 1 cc graduated pipet into the respective *A*, *B* and *C* tubes. Remove tubes from the water bath, close the tube with the palm, shake quickly and return to the water bath. Then add 0.5 cc of tenth-normal sodium hydroxide to each tube from a buret and shake. As soon as the dark pink changes to light add the final 5 cc of tenth-normal sodium hydroxide. Note the exact time when the very light pink of the control or of the original emulsion or a light yellow-brown containing no pink is reached. Record the total time required for the reduction of the 1 cc of tenth-normal sodium hydroxide in minutes and fractions.

If the time for return to neutrality is ten minutes or over, do not record results as final. Repeat the aforementioned procedure but wait three minutes after the delivery of the duodenal fluid before adding the first 0.5 cc of tenth-normal sodium hydroxide. Through this slight change in technic a slowly active tryptic ferment has been found to fall within figures of clinical significance when previously it would have been reported as greatly delayed or completely absent.

Lipolytic Activity—For trypsin the aforementioned procedure is used, with the following exceptions. Use only 0.1 cc of *A*, *B* and *C* duodenal fluids, always

wait three minutes,⁶ then add 0.5 cc of tenth-normal sodium hydroxide, wait until the mixture completely loses its pink color before adding the final 0.5 cc of tenth-normal sodium hydroxide. Record exactly the time of adding the duodenal juice, and the time when the mixture with the added 1 cc of tenth-normal sodium hydroxide has lost every trace of pink color or returned to its original neutrality. If in ten minutes the result is negative, repeat the test, but use 0.5 cc of duodenal fluid. Multiply the time figures by 5.

Time figures of five minutes or less for the formed amino acids and fatty acids to neutralize 1 cc of tenth-normal sodium hydroxide are considered normal concentrations of tryptic and lipolytic enzymes, respectively.

Five Per Cent Starch Solution—Stir 25 Gm of Merck's soluble starch (Lintner) into a smooth paste in a mortar by adding slowly 30 cc of cold distilled

TABLE 3—*Enzyme Concentration in Five Cases of Diabetes*

Case	Trypsin			Lipase			Amylase		
	A	B	C	A	B	C	A	B	C
	Minutes			Minutes			Gm of Maltose		
1	9	20+	14½	4¼	6	4¼	0.27	0.14	0.23
2	20	12	0	16¼	10¼	30	0.15	0.19	0.00
3	40	0	20	27½	12	4½	0.30	0.15	0.25
4	3¾	5½	13	4½	4½	4½	0.35	0.25	0.27
5	10	15	12	3½	3½	3½	0.35	0.23	0.21

TABLE 4—*Enzyme Concentration in Patients of Normal Weight*

Diagnosis	Trypsin			Lipase			Amylase		
	A	B	C	A	B	C	A	B	C
	Minutes			Minutes			Gm of Maltose		
Giardiasis	7	5	5½	3½	—3	—3	0.42	0.42	0.37
Gallbladder adhesions	0	9¾	5¼	0	—3	—3	0.40	0.19	0.30
Hypochlorhydria	9½	7	7½	3¼	—3	—3	0.37	0.42	0.37
Hyperchlorhydria	4½	4½	4¼	—3	—3	—3	0.37	0.23	0.15
Hypochlorhydria, gallbladder adhesions	0	7	12	4¼	3	3¼	0.40	0.27	0.30
Gallbladder stasis		6½		4½	—3	—3	0.30	0.27	0.27

water. Heat to boiling 470 cc of distilled water in a 500 cc pyrex sterile flask. Pour gradually into starch paste, stirring continuously to insure a mixture free from lumps. Pour the solution back into the warm pyrex flask. Add toluene to cover the starch solution with a ¼ inch layer. Keep at room temperature. Shake well before using.

6 Lipase is more sensitive to tenth-normal sodium hydroxide than is trypsin. When amounts as low as 0.1 cc of duodenal juice are used, one can conceive of a dilution of ferment so great that 1 cc of tenth-normal sodium hydroxide might disturb its activity, or even destroy it. The three minute wait permits the ferment to act in a neutral mixture or weakly acid one (formed fatty acids). Though many duodenal fluids have an active lipolytic ferment in high concentration, even in only 0.1 cc of the digestive fluid, later experience may bring a further modification in the technic, namely, the use of 0.5 cc of duodenal juice for both tryptic and lipolytic activity.

Five Per Cent Emulsion of Gelatin—Dissolve 25 Gm of Bacto-gelatin in 300 cc of distilled water in a 500 cc pyrex flask set in a water bath. Raise the temperature gradually until the gelatin is perfectly dissolved and clear. In a mortar place 12.5 Gm of acacia, U.S.P. (purest grade), add gradually 50 cc of liquid petrolatum, rub into a smooth paste, then add all at once 25 cc of distilled water, and continue stirring in one direction until a milk white emulsion is formed. To this add the 300 cc of melted gelatin. Pour into a graduated cylinder. Make up to 500 cc with washings of mortar and warm distilled water. Pour into a 500 cc sterile flask, add 3 cc of a 1 per cent alcoholic solution of phenolphthalein and make neutral (faint pink) with normal sodium hydroxide. Shake well, then distribute into storage flasks. Cover the emulsion in flasks with a thin layer of toluene, store in the ice chest. When needed liquefy by gentle heat in a water bath (a temperature of 60 C will scorch gelatin). Shake well to insure an even emulsion before measuring into test tubes.

Olive Oil Emulsion (20 Per Cent)—Place 25 Gm of acacia (purest grade) in a mortar, add gradually 100 cc of highest quality olive oil, rub into a smooth paste, then add all at once 50 cc of distilled water, and continue stirring in one direction until a milk white emulsion is formed. Add more distilled water, make up to 500 cc in a graduated cylinder, using washings of mortar with distilled water. Pour into a 500 cc flask. Add 3 cc of phenolphthalein and sufficient normal sodium hydroxide (about 1.5 cc) to make neutral or faint pink. Shake well to insure an even emulsion before pipetting into test tubes.

After considerable experiment it was found that dependable results were obtained only with freshly prepared oil emulsion. Formaldehyde as a preservative was not satisfactory, toluene with the oil emulsion gave larger figures for time or negative results. Sterilization also proved unsatisfactory. Further experimentation on this problem is being continued.

THE INSULIN SYSTEM

In their latest investigations, Depisch and Hasenohrl⁷ arrive at the following conclusions:

The assimilatory insulin system with its nervous regulation stands in the center of the carbohydrate metabolism. It promotes the absorption of sugar both in the liver and the tissues. In the liver this system is counteracted by the sympathetic nervous system and the secretion of the suprarenals, of the posterior lobe of the hypophysis, and of the thyroid (liver counter-regulation). In the tissues the effect of insulin is counteracted by the suprarenals and the thyroid (tissue counter-regulation). Independent of this hormonal regulation there appears to be also a direct influence of the nervous system on the sugar metabolism in the liver and tissues both promoting and checking it.

The glycogen-insulin mechanism is shown by Okada⁸ to be vital in the physiologic process of oxidation, as an incessant oxidation of sugar is unconditionally necessary to maintain the living process. The regulatory influence of this active sugar on the function of the digestive tissues is similar to that of oxygen on the function of the respiratory organs. A deficiency either of oxygen or sugar stimulates the vagus

⁷ Depisch, F., and Hasenohrl, R. *Klin Wchnschr* 9 345, 1930.

⁸ Okada, S., et al. *Pancreatic Function V The Secretory Mechanism of the Digestive Juices*, *Arch Int Med* 45 783 (May) 1930.

centers, lack of oxygen producing forced respiration, hypoglycemia, digestive hypersecretion, especially of pancreatic juice and bile, as well as hypermotility of the digestive tract

- The pancreas, the source of insulin, is the most important organ in the carbohydrate metabolism of the body. The external as well as the internal secretion plays a rôle of prime importance. According to Boldyreff,⁹ the uncombined pancreatic ferments are reabsorbed from the intestines into the blood and find their way to all tissues in the body. Their presence is required to explain many of the vital processes of a biochemical character in the cells and the tissues. Fischer¹⁰ also said "Ferments or enzymes . . . their participation is established in many, more exactly investigated, biological processes, and on that account we can with sufficient probability admit that they act in all vital processes of the body." Therefore the pancreas, with the aid of the intestinal juices and bile, not only provides the enzymes for the complete digestion of food in the alimentary canal, but likewise may prove to be the source of the cellular ferments that are indispensable not only for the general metabolism of the body as a whole, but for each particular cell's power of autolysis and synthesis, as well as digestion and assimilation of nutriment.

THE ACTION OF INSULIN

On Body Tissues—Most writers stress the retention of water along with the storage of glycogen in the cellular protoplasm and preceding the formation and storage of fat. Insulin activates the process of carbohydrate combustion in the tissues. The end-products of fat digestion cannot be fully utilized without the presence of such combustion. Oxygenation in the tissues cannot take place unless an adequate amount of dextrose is present. Meyer¹¹ pointed out that insulin accelerates carbohydrate metabolism by supplying an intermediary metabolism, namely, a capacity for depositing water in the cellular tissues. Feissly¹² attributes the retention of water to the increased hydrogen ion concentration of the plasma during the treatment with insulin, others, the need for water to effect carbohydrate storage. Vogt¹³ stated that under the influence of insulin, respiratory tests show increased carbohydrate metabolism and an increase of the fat formation from carbohydrates.

9 Boldyreff, W. N. *The Periodical Activity of the Organism and Its Physiological and Clinical Significance*, Read at Staff Meeting, Battle Creek Sanitarium, Feb., 1925.

10 Fischer, E. *Organische Synthesen und Biologie*, Berlin, 1908, p. 24.

11 Meyer, L. F., and Bamberg, K. *Recurrent Acetonemic Vomiting of Children, and Its Treatment with Insulin*, *Deutsche med. Wchnschr.* **51** 1100 (July) 1925.

12 Feissly, R. *Traitement insulinique des états de dénutrition chez les sujets non diabétiques*, *Presse méd.* **13** 196, 1926.

13 Vogt, E. *The Insulin Treatment of Nondiabetic Affections*, *Med. Klin.* **23** 169 (Sept 30) 1927.

The effect on hydrogen metabolism in water-impoveryished states, as in tuberculosis, is a fortunate secondary effect. The action of insulin is not a chemical one, because if the insulin is mixed with blood no glycolysis takes place. This is the reverse of the action of the external secretion of the pancreas, which reduces blood sugar probably through the action of a glycolytic enzyme.⁹ All investigations on the action of insulin prove that a disturbance of carbohydrate metabolism is the result of a diminished glycolysis rather than a consequence of increased glycogenesis. The chief action of insulin is, in fact, on the tissues and liver, so affecting them that in the presence of an excess of water and oxygen glycogen is synthesized and stored.

On Pancreatic Ferments—In their study, in 1929² of the humoral regulation of the gastric, pancreatic and biliary secretions, Okada and his associates definitely showed that the increased secretion of these juices, with increase of ferments and their activators, following the injection of insulin is marked in the presence of hypoglycemia, while it is nearly negative in the absence of hypoglycemia. Carusi¹⁴ found certain signs of a functional correlated action between the two pancreatic secretions, but could not assert that there exists a functional parallel action between the internal and the external secretions. He referred to the work of Monteleone, Kahn, Jones and Cammidge as separately finding a marked decrease in the activity of pancreatic ferment in diabetes and of Monteleone's use of insulin causing a considerable increase of enzymatic activity. Lambert and Hermann found in animals with fistula of the Wirsung canal no increase in the external secretion following an injection of insulin, probably because a hypoglycemia was not established. Insulin cannot be expected to stimulate external secretion in a pancreas with histologic alterations in its acinous part.

HUMORO-NEURAL FACTORS THAT GOVERN EXTERNAL PANCREATIC SECRETION

Gayet¹⁵ examined the secretions produced by electric stimuli applied to the pancreatic gland or to the vagus and also studied the secretions produced by secretin, injected either into the blood or into the duodenum. When direct electric stimulation was used, there was a prompt increase in the outflow of blood from the gland, which rapidly reached its maximum and which returned to the original level after the stimulation was discontinued. The flow of pancreatic juice followed an almost parallel course, but its onset and maximum were slightly retarded.

¹⁴ Carusi, R. Concerning Pancreatic Secretions, Policlin Roma (sez med) 37 90 (Feb) 1930

¹⁵ Gayet, R., and Guillaumie, M. The Reciprocal Quantitative Relations of the Secretion of Pancreatic Juice and Blood Stream, Compt rend Soc de biol 103 1216, 1930

When the pancreatic juice was stimulated with secretin, the output of the blood and the flow of juice were practically parallel, though the flow of juice persisted longer than the temporary increase in the outflow of blood. The increase in the flow of blood and of pancreatic juice showed the same reciprocal ratio after stimulation of the vagus. When atropine is injected into the saphenous vein the secretory response to direct stimulation of the gland is greatly decreased. Atropine had a more prolonged effect in decreasing the outflow of blood from the gland. Stimulation of the gland or vagus is affected through direct action of vasodilator nerve fibers. Hormone stimulation with secretin is explained by the theory of Bancroft, which concerns a local process determined by metabolites.

Physiologists who have studied the action of insulin in relation to blood reaction agree that this hormone, through its function of activating hydrogen, carbohydrate and fat metabolism, does aid in maintaining acid-base equilibrium and a high blood alkali reserve. Arschawsky¹⁶ studied the influence of the change in the reaction of the blood on the secretion of the pancreas and concluded

1 An increase of the p_H and CO_2 values of the blood enhances the stimulating effect of HCl on the secretion of the pancreas. 2 The stimulating effect of secretin upon pancreatic secretion is enhanced by an increase of p_H and CO_2 values of the blood. 3 A decrease of the normal p_H and CO_2 values of the blood inhibits the stimulating effect of HCl on external pancreatic secretion, but not that of secretin. 4 A change in the p_H and CO_2 of the blood is accompanied by a change in the CO_2 content alone, of the pancreatic juice.

Rosenkow¹⁷ reported his results with pilocarpine and secretin before and after vagotomy. Pilocarpine has a stimulating influence on the vagal terminals. Pilocarpine becomes ineffective following vagotomy, whereas secretin stimulates effectively pancreatic secretion. In normal animals, secretin stimulates the secretion of an inactive pancreatic juice, but after vagotomy the secretion is able to split proteins (tryptic activity). The morphologic changes in the pancreas following vagotomy are expressed in an enlargement of the secretory granules and a decrease in their number, the protoplasm of the glands containing numbers of vacuoles and large secretory droplets. Therefore, the amount of pancreatic juice depends on the number of granules in the gland cells, a decrease of secretory activity is accompanied by a decrease or disappearance of granules. Rosenkow expressed the belief that pilocarpine becomes ineffective as a secretagogue after vagotomy, not because it is no longer able to act on the nerve terminals, but because it exerts a toxic action on the gland cells themselves. When the neural stimulation to secretory activity is destroyed by vagotomy, the humoral stimulant, secretin, appeared to have

16 Arschawsky, J. A. The Influence of the Change in Blood Reaction on the Secretion of the Pancreas, *Arch f d ges Physiol* **224** 128, 1930.

17 Rosenkow, I. P. Effect of Vagotomy on Secretory Activity of the Pancreas, *Arch f d ges Physiol* **223** 146, 1929.

a more potent effect in that the pancreatic juice previously inactive possessed tryptic activity. It is now recognized that the pancreas can secrete a proteolytic ferment, trypsin, as well as its precursor, trypsinogen. Rosenkow concluded that after vagotomy this activation is especially enhanced by the great enlargement of the secretory granules, even though decreased in number. Therefore, the vagi can be said to exert on the gland cells of the pancreas a trophic influence, by maintaining a definite equilibrium in the metabolism of the cells.

CONCLUSIONS

1 Injections of insulin twice daily to the average total amount of 40 units produced in a selected group of eighteen patients with malnutrition a definite, measurable increase in the concentration of pancreatic ferments recovered from the duodenum during fasting.

2 Accompanying this effect, there appeared in a number of the patients a return to a normal sequence of so-called A, B, C bile fractions, in other words, the function of the biliary tract, together with external pancreatic functions, was improved.

3 The methods employed in the estimation of enzyme concentration satisfy the essential laws of enzyme action, besides confining normal figures within narrow limits, and thus making a sharp division between high and low concentration, especially of trypsin and lipase.

4 Tests for blood sugar tolerance are required to eliminate patients with hypoglycemia as unsafe for insulin therapy in malnutrition.

5 Studies of the stool before and following insulin therapy gave results that showed a direct parallel between the more complete digestion and assimilation of food elements and the increased concentration of pancreatic ferments.

6 The aforementioned findings appear to the authors as justifiable proof that the cause of the striking gain in weight in most of the eighteen patients receiving insulin therapy was due in part to the stimulating effect of insulin on external pancreatic secretion and bile and in part to a resulting normal digestion and assimilation of aliment.

Miss S. A. Lehmann, R.N., collected the duodenal fractions and made the basal metabolism studies; Miss J. L. Yates, dietitian of the outpatient department, taught the clinic patients the use of the syringe and the insulin, and gave individual instruction as to diet and relief from hypoglycemic symptoms and prepared the printed slips containing the diet and the measures for symptomatic relief; Miss Mildred Carlisle, pharmacist, gave her assistance in the preparation of the substrates, and the laboratory technician, Miss M. E. Watson, co-author of this paper, made hundreds of estimations of pancreatic enzymes before she was satisfied that the technic was reliable.

Book Reviews

The Treatment of Asthma By A H Douthwaite, M D, F R C P (Lond)
Price, \$2 50 Pp 160 New York William Wood & Company, 1930

In a small book of 160 pages the author attempts an up-to-date discussion of the diagnosis and treatment of the asthmatic patient. The material presented is fairly well handled, but the arrangement allows much repetition. The book is divided into two parts, the first dealing with theoretical, clinical and laboratory aspects of asthma and the second with therapeutics. The bibliography indicates that European literature has been the chief source of reference. The classification of asthmatic patients into primary and secondary groups depending on the age of onset and certain biochemical differences does not clarify or simplify the problem. The discussion of clinical features and pathology is very brief and elementary. As emphasized by the author, some of the metabolic and bacteriologic findings that are given must be corroborated before being accepted as significant. The following chief etiologic factors that produce attacks are discussed: allergens, local irritants, reflex stimulation, psychic influences and endocrine excitants. In the chapter on "Preliminary Investigations," proper emphasis is placed on the necessity of a complete study.

The second part of the book is devoted to a discussion of most of the modern forms of treatment. The uses and limitations of these forms of treatment are discussed. Special emphasis is placed on the value of physical therapy and on the administration of vaccine.

In the concluding chapter, the following apt paragraphs are given:

"Elimination of focal sepsis and suspected sources of reflex vagal stimulation seldom produces striking results."

"The majority of drugs are of use merely to hold symptoms in check and have no value in eliminating or correcting the asthmatic tendency."

"In no other disease is greater concentration on detail demanded of the physician. In no other illness are we so often disappointed when victory seems to be ours. Yet when we look back on the fruit of the labours of the past twenty years we cannot but be impressed by the material advance which has been made towards the ultimate conquest of this mysterious malady."

The Practice of Medicine By A A Stevens Third edition Cloth Price, \$8, net Pp 1150, with illustrations Philadelphia W B Saunders Company 1931

The new edition of Stevens' "Practice of Medicine," while retaining the briefer one volume form of previous editions as compared to the more bulky systems, and adhering to the general form of presentation made familiar by Osler's single volume textbook, has been thoroughly deleted of all work not in accord with modern conceptions of medicine and has been brought thoroughly up to date.

In the broader subjects, such as pneumonia and typhoid, extensive revisions and additions have been made, giving a thorough contemporary presentation of those subjects. A great many sections have been completely rewritten, including those on such diseases as icterus, ulcerative colitis, agranulocytic angina, nephrosis,

the anemias, coronary occlusion and undulant fever, to mention a few representative cases. New subjects include psittacosis, toxoid prophylaxis of diphtheria, immunization to measles, antitoxin in erysipelas, parathyroid dysfunction and others of equal interest.

The subject matter is divided under the headings of infectious diseases, intoxications, deficiency diseases, disorders of metabolism and diseases according to the systems: digestive, respiratory, circulatory, renal, blood-forming, spleen, ductless glands, joints and bones, muscles and nervous system. Each topic is then dealt with in the orthodox manner, giving first a descriptive definition, historical data, etiology, including specific and predisposing factors, morbid anatomy, symptoms, signs, complications, and therapy.

The work appeals as a strictly modern, conservative and carefully planned and executed handbook for both students and physicians. All material is quickly accessible, and there is no evidence that the restriction to one volume makes it in any way limited in its scope.

A Clinical Study of Addison's Disease By Leonard G. Rowntree, M.D., and Albert M. Snell, M.D. Cloth. Price, \$4, net. Pp. 317, with 41 illustrations. Philadelphia: W. B. Saunders Company, 1931.

From a group of "approximately 300 cases in which a diagnosis of Addison's Disease (definite or tentative) had been made during life, or extensive lesions of the suprarenal gland have been found at necropsy," records of 108 patients have been selected and form the basis for this presentation.

While one is not convinced from the case reports that the diagnosis is indisputable in each instance, the authors have had a most unusual opportunity to study and treat this rare malady. Their compilation is particularly fortunate at this time, now that Swingle and Pfiffner and others have isolated a cortical hormone which gives every promise of as much ultimate success in the treatment for Addison's disease as insulin has had in the treatment for diabetes mellitus.

The history of the development of knowledge of Addison's disease before the classic description of Addison (which is reprinted in full) and the modern conceptions comprise the early chapters. Then follow the presentation of necropsy material, case reports, chapters on signs and symptoms, laboratory data, diagnosis, complications, prognosis, treatment, including the recent results in a few cases in which the patients were treated with the cortical hormone of Swingle and Pfiffner, and finally a short chapter on "statistical considerations." An excellent bibliography and index are appended.

This monograph should be in the library of every physician.

Les malades dits imaginaires By M. Nathan. Price, 14 francs. Pp. 134. Paris: Gaston Doin, 1931.

In this short monograph, one of a series on practical medicine, the author discusses the diagnosis and treatment of so-called imaginary illnesses from a critical point of view. He first points out the dangers of such a diagnosis, giving examples of conditions that in the past were considered as functional and are now known to have an organic basis. The necessity for thorough examination for evidences of organic disease is stressed. In subsequent chapters he discusses the various forms of functional diseases and the possible associated organic conditions. The last chapter is devoted to a very brief discussion of therapy in which the author stresses the point that the type of therapy must vary with the type of case.

The book is obviously intended only as a brief and rather superficial survey of the subject matter and seems to fulfil these qualifications.

THE NORMAL RANGE OF GASTRIC ACIDITY FROM YOUTH TO OLD AGE

AN ANALYSIS OF 3,746 RECORDS *

FRANCES R VANZANT, M D †

WALTER C ALVAREZ, M D

GEORGE B EUSTERMAN, M D

HALBERT L DUNN, M D

AND

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At first glance it would seem inconceivable that for sixty years physicians could have gone on studying gastric acidity in the sick, without, somewhere along the way, pausing to secure standards of normal. There are two explanations for this peculiar behavior of the medical profession—one, that we have always been more ready to study disease and to treat it than to make the basic anthropologic and statistical studies that would enable us to say where normal ends and disease begins, and the other, that it is not easy to get several thousand normal persons to submit to gastric intubation.

Much work has been done with medical students and with infants, but, unfortunately, most of the published reports of these studies are useless for statistical analysis because distribution tables were not supplied, and measurements from several age groups were averaged together.

Although the literature on gastric analysis is enormous, we have been able to find only a few papers that throw light on the way in which the acidity of the gastric contents varies from youth to old age. The best of these is by Polland and Bloomfield,¹ who studied 90 patients recovering from injuries or diseases other than gastro-intestinal. They used histamine as the stimulus to gastric secretion, and found what appear to be straight line (inverse) relations between the amount and the acidity of the secretion and age. Obviously the group studied is too

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† Fellow in Medicine, the Josiah Macy, Jr., Foundation, on duty in the Mayo Foundation.

1 Polland, W. S. and Bloomfield, A. L. Normal Standards of Gastric Function, J Clin Investigation 9:651 (Feb) 1931

small for a detailed analysis of the problem, but this need not lessen the gratitude of the medical profession to the authors for the excellent start that they have made. Valuable data on the influence of age, sex and physical fitness on the incidence of achlorhydria are to be found in an article by Bloomfield and Keefer²

To those who may now be asking "But why bother so about standards of normal?" our answer is "Why bother about standards of normal for basal metabolism or for any other measurable function of the body?" Here, let us say, is a woman of 50 years with achlorhydria, is it a disease about which we should become anxious, or is it a symptomless peculiarity of every fourth normal person of that age? A few months ago, when we began this study, we could not have given an answer to this question, today, we think we can

TYPE OF CASE USED IN THE PRESENT STUDY

It occurred to us that every year in a large institution like the Mayo Clinic hundreds of practically normal persons submit to gastric analysis because they have a few symptoms suggestive of cholecystitis, pernicious anemia, migraine or ulcer. In many cases, probably, if the physician who first saw the patient had taken a more careful history, he would have recognized the functional nature of the few digestive disturbances and would not have bothered to order a gastric analysis.

Accordingly, one of us (Dr Vanzant) reviewed 16,000 records of patients (registered in the years 1928 to 1931) who submitted to gastric analysis, picking out for special study 3,381 (as will be explained later, 365 additional cases were reviewed from the literature) in which the absence of symptoms suggesting serious disease and the inability of the medical examiner and the roentgenologist to show anything wrong with the stomach, duodenum, gallbladder or colon seemed to justify the diagnosis of a normal digestive tract. Furthermore, all cases were excluded in which the patient was accustomed to the use of alcohol or in which there was serious disease such as syphilis, advanced cardiovascular-renal incompetency, anemia, leukemia, jaundice, thyrotoxicosis, myxedema, infectious arthritis, tuberculosis, Addison's disease, infestation with intestinal parasites, diarrhea, disease of the liver or pancreas or appendicitis. In addition, all cases were excluded in which there was severe malnutrition or in which the patient was recovering from serious illness of any kind.

The diagnoses made in most of the accepted cases were fatigue, or anxiety, neurosis, migraine, constipation, negative findings, irritable bowel or mucous colitis. In many cases an analysis of gastric secretion

² Bloomfield, A. L., and Keefer, C. S. Gastric Acidity: Relation to Various Factors Such as Age and Physical Fitness, *J. Clin. Investigation* 5: 285 (Feb.) 1928

was made because the patient complained of the occasional presence of paresthesia, sore tongue, abdominal pain or tenderness, bad breath or belching

HOMOGENEITY OF THE DATA

After our study was almost completed we reviewed the data and picked out a large group of cases in which it seemed as if there could be no question about the normalcy of the person studied, we compared the distribution polygons of this group with the ones that we had already obtained and found them to be almost identical. This discovery greatly encouraged us in our belief that we have succeeded in obtaining data from fairly normal persons.

It was easy to find enough patients within the range of middle age, and we stopped collecting them as soon as we had enough to give smooth distribution curves such as are presented in chart 1. After that, many thousands of records had to be searched before we could find a sufficient number of apparently healthy old men and women with few symptoms and negative findings.

We found so few persons with ages less than 20 years that a satisfactory statistical analysis of their measurements could not be made. We, therefore, searched the literature³ for gastric analyses made on presumably normal children and youths, and were able to find 365, 203 of these persons were girls and 162, boys. In all cases the test meal used was of the Ewald type. We used the data thus obtained to fill the gap in our material.

TECHNIC OF GASTRIC ANALYSIS

The test meal used at the Mayo Clinic consists of eight arrowroot cookies and 400 cc of water. After one hour a sample of the gastric contents is removed with the Sawyer tube, it is tested for free acid, and if this is present the stomach is emptied and the tube is withdrawn. If, however, there is no free acid, the tube is left in and three more samples are removed at intervals of fifteen minutes. The results of titration are expressed in the usual terms of cubic centimeters of tenth-normal sodium hydroxide required to neutralize 100 cc of gastric juice.

For the purposes of this paper we have in every case used the figures for total and free acid obtained at the end of the first hour. The only use made of subsequent readings with the fractional test was to help us in distinguishing between true

3 Jacobsen, A. T. B. Some Investigations Concerning the Gastric Secretion in Children of 1 to 4 Years Suffering from Diseases of the Stomach and Intestines, Together with Some Remarks as to Treatment, *Acta med. Scandinav.* **52**: 773, 1920. Klementsson, Emil. Recherches sur le suc gastrique chez les enfants de 1 à 12 ans, *Acta pædiat.* **3**: 136, 1923. Muhl, Greta. The Secretion of Hydrochloric Acid in Normal Conditions and in Chronic Gastric Affections of Children from 1 to 13 Years of Age, *Acta pædiat.* **4**: 356, 1925. Wright, C. B. Gastric Secretion, Gastro-Intestinal Motility and Position of the Stomach in a Group of 250 Children of the Lymanhurst School, *Arch. Int. Med.* **33**: 435 (April) 1924.

and false achlorhydria. All data from persons who did not show free acid at the end of the first hour have been segregated into a group which is represented by the lines corresponding to abscissa zero in chart 1, and by the small polygons in chart 2.

INCIDENCE OF ACHLORHYDRIA

The first thing that struck us when we arranged our data in the form of percentage distribution tables and polygons (table 1 and chart 3) was the remarkably high incidence of achlorhydria and the steady increase of this incidence with age.

In table 1 all cases in which free acid was not obtained on the first aspiration at the end of an hour are listed under the heading of apparent

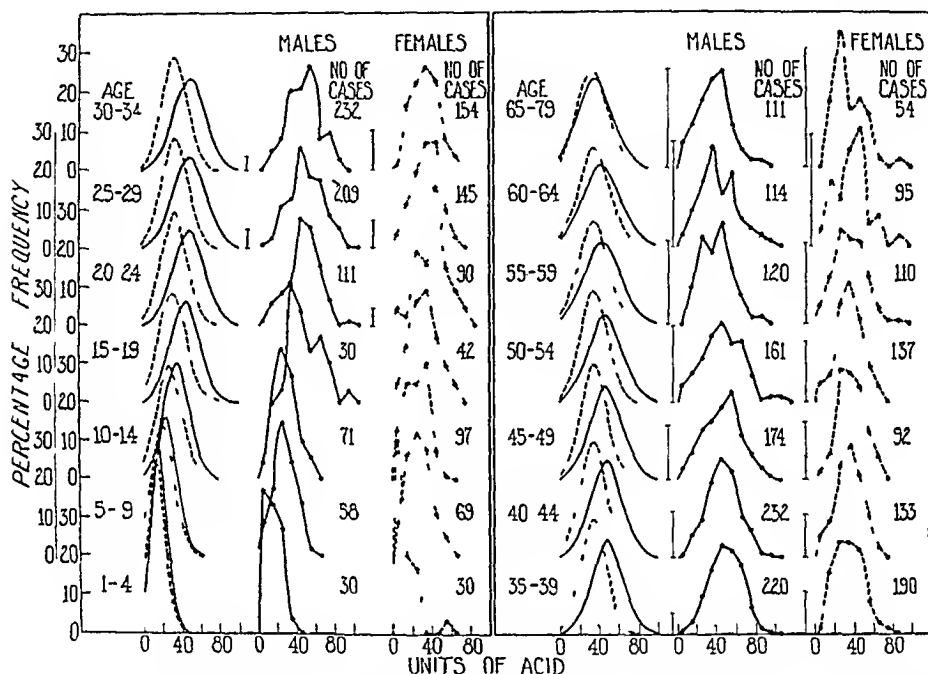


Chart 1.—The polygons represent the frequency with which free hydrochloric acid of different concentrations was found in males and females at different ages. For convenience of spacing on the page, the polygons representing data from older subjects have been placed to the right instead of above those representing data from the younger subjects. In both halves of the figure the polygons in the second and third columns represent the actual data. The first column represents these polygons smoothed. The vertical lines drawn to the left of a number of polygons in the second and third columns represent the percentages in the group of subjects with achlorhydria.

achlorhydria. If free acid did not appear either on repeated fractional analysis or after the injection of histamine, the patient was considered to have what for convenience we will call true achlorhydria. Unfortunately the control study with histamine was made in only a small percentage of the cases. It will be noted that in most of the cases in which free acid was absent at the first aspiration it remained absent in subsequent samples.

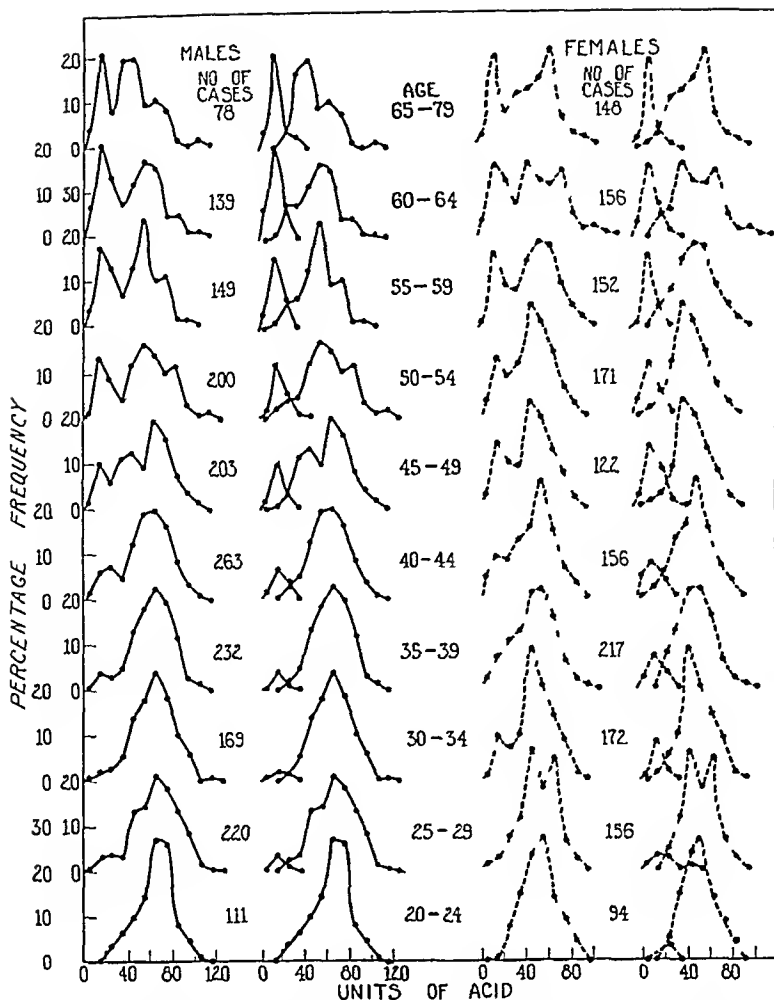


Chart 2—The polygons in the first and third columns represent the frequency with which total acidity of different concentrations was found in men and women at different ages. The bimodal nature of the polygons suggested the presence of two groups of persons, one with and the other without free acid, and in the second and fourth columns the distributions of data from these two groups are shown separately.

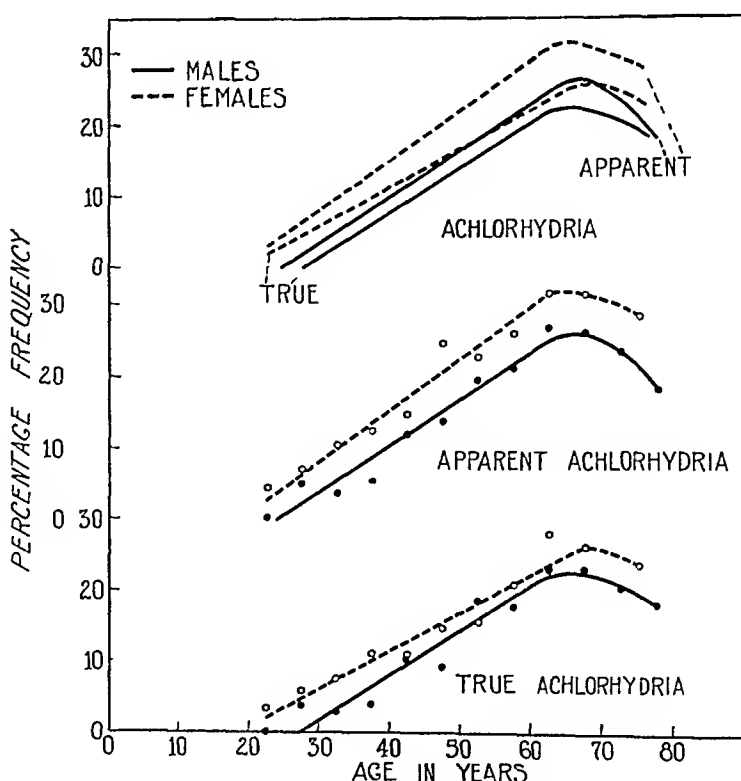


Chart 3—The curves show the relation between the incidence of achlorhydria and age.

It should be noted that we have carefully avoided the use of the term "achylia" which we think should probably be used only in those cases in which the stomach is dry and in which repeated injections of histamine fail to produce any secretion. We doubt even if there is any real difference between what we have called true and probable achlorhydria. In both there is some secretion of acid and the only difference is that some of it is more deeply submerged by the neutralizing fluid.

Chart 3 shows that for both true and apparent achlorhydria there is from youth to about the age of 65 years in both sexes a straight-line correlation between the incidence of the defect and age. After the age of 65 years there appears to be a definite falling off in the amount of achlorhydria, possibly because the persons with achlorhydria are not so hardy or long-lived as are those who have a strongly acid gastric juice.

TABLE 1—*Achlorhydria*

Age, Years	Males				Total Cases	Females				Total Cases
	Apparent Achlorhydria		True Achlorhydria			Apparent Achlorhydria		True Achlorhydria		
	Cases	Per Cent	Cases	Per Cent		Cases	Per Cent	Cases	Per Cent	
20-24					111	4	4.3	3	3.2	94
25-29	11	4.9	8	3.6	220	11	7.0	9	5.8	156
30-34	6	3.5	5	3.0	169	18	10.4	13	7.6	172
35-39	12	5.2	9	3.9	232	27	12.4	24	11.1	217
40-44	31	11.8	27	10.3	263	23	14.9	17	10.9	156
45-49	29	13.7	19	9.3	203	30	24.6	18	14.8	122
50-54	39	19.5	37	18.5	200	34	22.8	27	15.8	171
55-59	32	21.2	27	17.8	152	39	26.2	31	20.8	149
60-64	42	26.9	36	23.1	156	44	31.6	39	28.1	139
65-69	27	26.2	24	23.0	103	18	31.6	15	26.3	57
70-74	8	23.5	7	20.6	34	6	28.6	5	23.8	31
75-79	2	18.2	2	18.2	11					
Total	239	12.9	200	10.8	1,854	254	17.4	201	13.8	1,454

It is curious also that at all ages the women show a greater tendency to achlorhydria (about 3 per cent on the scale) than do the men. Strange to say, in our series of cases at the Mayo Clinic there was no instance of true achlorhydria in the 111 men aged from 20 to 25 years. In women the incidence of true achlorhydria varied from 3 per cent at the age of 20 years to 28 per cent at the age of 60 years. In men the highest percentage of achlorhydria was 23 at the age of 60 years.

INCIDENCE OF ACHLORHYDRIA AS OBSERVED BY OTHERS

Kelling¹ found free acid absent in 15 per cent of 2,031 men and in 19 per cent of 1,116 women examined. He took care to exclude only the organic gastric and duodenal diseases and he did not segregate his

¹ Kelling, G. Statistisches über Salzsauremangel im Magen, Arch f. Verdauungskr. 15 568, 1909.

cases according to age. Conner,⁵ at the Mayo Clinic, found achlorhydria in 14.6 per cent of 691 men and in 20.4 per cent of 509 women of all ages. He took a consecutive series of reports from the laboratory in which gastric analyses are made and did not attempt to exclude cases of serious organic disease. With a smaller group of cases in England, Bell⁶ obtained figures of 13.8 per cent for men and 16.1 per cent for women. Bennett and Ryle⁷ found achlorhydria in 4 of 100 apparently healthy students. A similar figure has been obtained by a number of investigators who have studied young men and women.

Muhl did not find a single case of achlorhydria in 40 normal children, and Klumpp and Neale⁸ were also unable to find any instance of this abnormality in 80 children studied. Wright, however, found 4 per cent of 230 apparently normal children to be without free hydrochloric acid.

Conditions are different in the aged; Seidelin⁹ found free acid absent or very low in 40 per cent of aged persons. He studied Danish people of the working classes, aged more than 50 years. Dedichen¹⁰ found anacidity in 66 of 99 apparently healthy men and women in an old people's home in Copenhagen. Davies and James,¹¹ with the usual test meal and fractional analysis, failed to find free acid in 32 of 100 normal persons aged more than 60 years. With histamine, they obtained acid in 13 of the 32.

The fact that our figures are lower than those published by other observers leads us to hope that we have been more successful in excluding cases in which the abnormality was due to disease. It may be, however, that the incidence of achlorhydria varies with different races and in different climes.

NORMAL RANGE OF FREE ACID IN MEN AND WOMEN

The data on which this study is based are presented in table 2 and chart 1. There it will be seen that after the earlier years of life the

5 Conner, H. M. Hereditary Aspect of Achlorhydria in Pernicious Anemia, Study of Gastric Acidity in 154 Relatives of 109 Patients Having Pernicious Anemia, *J. A. M. A.* **99** 606 (March 1) 1930.

6 Bell, J. R. Notes on a Consecutive Series of 425 Gastric Analyses by the Fractional Method, *Guy's Hosp. Rep.* **72** 302 (July) 1922.

7 Bennett, T. I., and Ryle, J. A. Studies in Gastric Secretion. V. A Study of Normal Gastric Function, Based on One Hundred Healthy Men by Means of the Fractional Method of Gastric Analysis, *Guy's Hosp. Rep.* **71** 286, 1921.

8 Klumpp, T. G., and Neale, A. V. The Gastric and Duodenal Contents of Normal Infants and Children, *Am. J. Dis. Child.* **40** 1215 (Dec.) 1930.

9 Seidelin, quoted by Faber.

10 Dedichen, Lucien. Anacidity in Old Persons, *Acta med. Scandinav.* (supp.) **7**:345, 1924.

11 Davies, D. T., and James, T. G. I. An Investigation into the Gastric Secretion of a Hundred Normal Persons Over the Age of Sixty, *Quart. J. Med.* **23** 1 (Oct.) 1930.

TABLE 2—Free Acid

Group	Units of Acid	Males																		Females																	
		Age, Years																		Age, Years																	
		14	59	10	11	15	19	20	21	23	29	30	31	35	39	40	44	45	49	50	51	55	59	60	64	65	Total										
No free acid	0	1	2							11	6	12	31	29	39	32	42	37	242	4	2			2	4	11	18	27	23	30	31	39	44	21	262		
with free acid	1	9	11	5	3	1	1	2	1	5	7						3	7	46	18	6	12	2	2	5	2	3	7	2	6	5	4		74			
	10	10	10	14		6	5	8	6	13	12	12	11	10	12	11	10	12	129	6	18	24	6	17	16	25	30	12	6	9	13	15	9	206			
	20	29	8	20	24	1	9	22	13	22	22	18	26	18	19	243	18	19	243	5	22	24	11	14	28	34	45	31	26	34	26	11	19	130			
	30	39	1	14	19	9	12	26	31	36	44	26	27	22	29	25	223			19	29	10	32	39	41	45	38	25	42	21	23	8	375				
	40	49		8	7	7	30	53	34	50	58	32	32	31	15	27	384			4	7	7	13	39	35	41	28	17	29	23	28	9	250				
	50	59		1	4	4	28	38	43	47	51	39	24	17	21	12	329	1		1		1	4	8	14	12	17	14	11	12	13	5	7	119			
	60	69			5	17	36	13	39	24	20	25	9	8	5	201							2	4	4	5	6	3	5	5	4	7	1	46			
	70	79			3	7	17	15	15	16	12	11	2	5	2	103																		4			
	80	89														32																		4			
	90	99			1	1	1	1	1	1	2	1	2	3	2	9																		1			
	100	100														3																		4			
Total		30	58	71	30	111	209	163	220	232	174	161	120	114	111	1,804				30	69	97	42	90	145	154	190	133	92	137	110	93	54	1,438			
Median		110	220	227	470	490	495	484	490	462	469	450	403	390	386					83	248	252	330	338	362	339	338	343	350	346	346	376	295				
Mode		127	115	261	396	505	473	494	495	464	422	443	406	326	362					09	251	302	294	330	338	323	346	328	333	333	394	207					
Mean		147	272	235	507	482	506	479	488	463	493	454	402	422	368					120	246	227	321	336	353	310	345	342	361	349	353	367	339				
Probable error of mean		11	11	10	20	10	08	09	07	07	09	11	10	12	11					12	09	09	16	10	08	07	07	08	10	08	11	12	14				
Standard deviation		87	118	121	162	162	175	164	163	162	167	205	158	196	175					94	105	132	149	138	136	135	142	138	137	134	162	167	153				
Probable error of standard deviation		08	07	07	14	07	06	06	05	05	06	08	07	09	08					08	06	06	07	07	05	05	05	06	07	06	07	08	10				
Coefficient of variability		59.3	43.3	42.4	32.0	33.5	34.5	34.2	33.5	35.0	33.8	45.6	39.3	46.4	47.5					78.2	42.8	58.1	46.3	41.0	38.6	39.6	41.2	40.4	38.0	38.5	45.9	45.6	45.0				

distributions become more and more bimodal owing to the existence of two types of human beings, one with free acid and the other without. That these groups are distinct is shown also by the bimodality of the distribution polygons representing total acidity (chart 2).

For a number of reasons it seemed best to make two different distribution polygons for the two groups of data. In the first place, it did not seem to be good statistical practice to group all the figures from achlorhydric persons opposite the one abscissa of zero because the stomachs of these persons secrete varying amounts of acid although it is more or less deeply submerged by the diluting fluid, even though it does not appear as free acidity. Furthermore, with the data from all (apparently and actually) achlorhydric persons excluded, we were left with fairly symmetrical and typically shaped distribution curves which lent themselves easily to smoothing and to other forms of mathematical treatment.

It should be noted that in chart 1 the first four polygons (ages from 1 to 20 years) represent mainly data secured from the literature. The other polygons represent data collected at the Mayo Clinic. The first series shows smoother curves representing, for men and women, percentage distribution of the figures as they probably would appear if a sufficiently large number of observations had been available for study. To get these curves, the means and standard deviations of the data obtained from patients with free acid were plotted as in chart 4. Curves were then fitted through the points to represent the most probable location of means and standard deviations. With these corrected or smoothed values as a basis, "normal," "cocked hat" curves were then drawn. In most instances they closely followed the actual data.

The second and third columns in chart 1 show for men and women, respectively, the actual percentage distributions of acid values at different ages. The length of the line drawn to the left of each polygon represents the percentage of cases of apparent achlorhydria in each of the age groups. The polygon represents the percentage distribution of the cases that were left after the achlorhydric ones were removed. In them, the sum of the ordinates is 100.

The first set of polygons shows, first, that the free acid of the stomach increases rapidly through childhood and up to the age of 15 years. Careful mathematical treatment of the measurements made on young persons indicate that there is an inflection of the line such as is shown in the chart representing mean acidities (chart 4). After this time there appears to be no definite change of the mode in women until the age of 65 years, and in men until the age of 45 years. About the age of puberty the modal value for boys begins to rise above that for

girls, and by the age of 25 years there is a difference of about 12 points. This difference begins to diminish at the age of 40 years owing to a decrease in the modal value for men.

The theoretical modes were located by two methods which were found to check fairly closely. In one method we used Pearson's empiric formula which relates the mode to the mean and the median, and in the other we determined the distance from mean to mode by multiplying the index of skewness by the standard deviation.

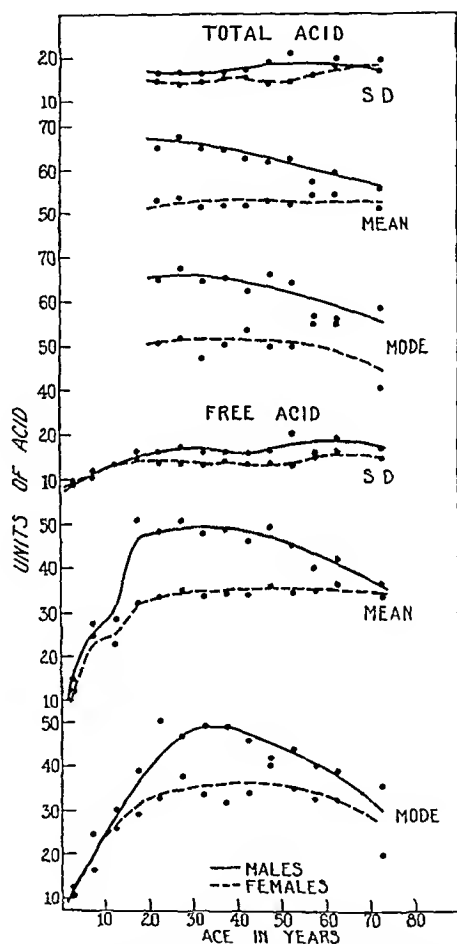


Chart 4—The curves show the means, calculated modes and standard deviations for free and total hydrochloric acid in males and females at different ages.

The changes in the modes for men and women are shown more clearly in chart 4, where it will be seen that the modal free acidity in men decreases steadily after the age of 40 years. We cannot be sure that it falls off in women because there were only 54 women in the group aged 65 years or more. If we were to discard this one datum a straight line could be drawn in chart 4 just as it can be drawn through the data representing the mean free acidity (in women) from youth to old age.

The sameness of free acidity in old men and women can be seen also from the fact that the two smoothed curves at the top of the first column in the second half of chart 1 are almost identical and closely overlapping

A study of the polygons in chart 1 shows a slight widening for men after the age of 50 years and for women after the age of 55 years. This is shown again graphically in the curves representing standard deviation

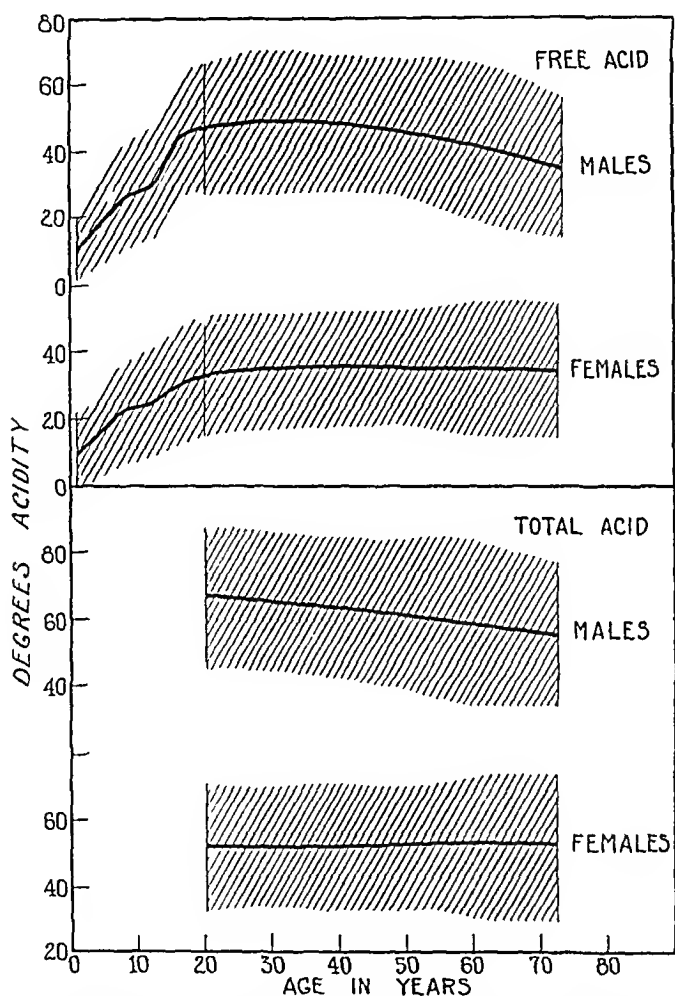


Chart 5—Standards of normal. The shaded areas represent the limits within which lay 80 per cent of the data for free and total acid at the different ages. The heavy lines represent modes.

(chart 4) It is a remarkable fact that one can occasionally find free acid of 80 and more in apparently normal old men and women.

It is easy to say that the total range in our cases is from 0 to 108, but it is not so easy to say where one should place the limits of normal. It does not seem probable that with all our care in selecting the records for study, all of them came from normal persons. In chart 5 we have plotted for men and women modal free acidity at the different ages and on each side of these curves we have drawn other lines representing the

limits within which lie 80 per cent of our data. We might just as well have drawn other lines delimiting other fractions of the material, but so far as we know, there is no scientific reason for placing limits of normal at one point rather than at another.

TOTAL ACIDITY

The variations in total acidity can be studied in table 3 and chart 2. There it can be seen again that the distribution polygons tend to be bimodal owing to the existence of two different types of human beings—one with more or less free acid in the gastric juice, and the other without. Data from the latter group are responsible for the secondary mode to the left of the main one, again it was thought advisable to separate the two groups of data just as we did while studying free acidity. In plotting two polygons in place of one we used as ordinates percentages of the total group of data obtained from persons with and without acid, or in other words, the sum of the ordinates of the two polygons in each pair is 100. We were unable to make a satisfactory study of total acidity in children because the published reports of gastric analyses are rarely so complete that one can split them into two groups of those from persons with and those from persons without free acid.

COMBINED ACIDITY

An analysis of the combined acidity shows that there is no significant variation at any age, and no difference between the sexes. The values ranged between 6 and 40 units with a mean about 17. The range was so small that 90 per cent of the data fell between limits of 12 and 22 units. The combined acid in persons with achlorhydria appears to be only slightly (1 unit) less than in persons with free acid.

COMMENT

We began this study with the vague idea that after middle age gastric acidity might gradually decrease, and that this decrease might be due to progressive atrophy of the mucosa similar to that which takes place in the skin. Actually, now, since we know that there is no falling off in gastric acidity in older women, it does not seem probable that the decrease observed in the men can be due to senile changes because if there were such, one would expect them to be equally marked in the women.

Similarly we can hardly ascribe the steady increase in the incidence of achlorhydria to atrophic changes that come with age because in that case we would expect the whole distribution curve of gastric acidity to move toward the left—that is toward lower values, and we would expect

TABLE 3—Total Acid

Group	Units of Acid	Males												Females											
		Age, Years												Age, Years											
		20 24	25 29	30 34	35 39	40 44	45 49	50 54	55 59	60 64	65 79	Total	20 24	25 29	30 34	35 39	40 44	45 49	50 54	55 59	60 64	65 79	Total		
With no free acid	1 9	1	1	1	1	4	3	3	1	5	3	22	2	2	1	5	7	3	6	5	9	3	41		
	10 19	7	3	3	9	17	20	24	24	24	28	156	1	4	14	15	11	16	19	24	27	16	147		
	20 29	3	2	2	2	10	6	11	7	11	5	57	3	4	3	7	5	10	9	10	8	3	62		
	30-39							1		2	1	4						1				2	3		
40 49														1								1			
Total		11	6	12	31	29	39	32	42	37	239	4	11	18	27	23	30	34	39	44	24	254			
With free acid	10 19						1	4			5			2			3	1	2	2	1		11		
	20 29	3	5	2	4	9	6	8	7	8	1	53	4	7	9	16	8	3	6	9	10	3	75		
	30 39	7	7	9	11	13	23	8	12	9	6	105	14	18	17	27	20	10	18	10	10	13	157		
	40 49	11	29	23	30	32	26	24	22	25	16	238	22	40	49	46	24	28	38	19	16	15	297		
	50 59	16	31	30	42	50	19	33	28	19	18	286	25	28	35	47	40	24	35	35	23	7	299		
	60 69	30	46	40	52	52	40	29	27	18	22	356	13	38	25	34	23	15	23	15	21	8	215		
	70 79	29	40	31	45	43	32	21	14	22	31	308	8	10	15	13	10	9	11	16	6	104			
	80 89	9	29	17	27	22	16	23	7	7	10	167	4	4	2	5	5	2	4	2	6	1	35		
	90 99	5	18	10	6	9	8	6	3	2	4	71				2			2		1	5			
	100 109	1	3		3	2	3	2		3	3	20													
110 119		1	1				3			1	6										1	1	2		
Total		111	209	163	220	232	174	161	120	114	111	1,615	90	145	154	190	133	92	137	110	95	54	1,200		
Median	65 8	67 1	64 4	64 4	62 3	63 0	61 2	56 8	57 9	56 5		52 0	52 7	50 0	51 2	52 5	51 7	51 3	54 3	54 5	47 4				
Mode	65 0	67 6	64 5	65 2	62 7	62 1	64 2	56 9	55 7	59 0		50 7	51 8	47 4	50 4	53 8	49 9	50 2	55 3	55 6	40 9				
Mean	64 6	66 9	64 3	64 0	62 1	61 0	62 0	56 8	58 9	55 3		52 7	53 1	51 3	51 6	51 8	52 6	51 9	53 8	53 9	50 9				
Probable error of mean	1 0	0 8	0 8	0 7	0 7	1 0	1 1	1 0	1 0	1 2	1 1		1 0	0 8	0 8	0 7	0 9	1 0	0 8	1 1	1 2	1 5			
Standard deviation	16 4	16 5	16 1	16 2	16 9	18 7	20 7	16 4	19 3	16 6		14 5	13 9	14 3	15 2	15 2	15 5	13 8	14 4	16 5	17 8	16 7			
Probable error of standard deviation	0 7	0 5	0 6	0 5	0 5	0 7	0 8	0 7	0 9	0 8		0 7	0 6	0 5	0 5	0 5	0 6	0 7	0 7	0 8	0 9	1 1			
Coefficient of variability	25 4	24 6	25 0	25 3	27 2	30 6	33 3	28 9	32 7	30 0		27 5	26 1	27 8	29 4	29 9	26 2	27 7	30 6	34 9	32 8				

to find some parallelism between this shift in both men and women and the increase in the incidence of achlorhydria. Actually there is no such parallelism in women and practically none in men.

Our impression, therefore, is that the process that gives rise to achlorhydria is different from the one which, in men, gradually reduces the degree of gastric acidity. There is much available evidence to indicate that the first process is inherited and that it partakes, perhaps, of the nature of mutation. Like many other defects, it can become uncovered at any time from birth to old age.

With the help of the data presented here, we hope to be able in future studies to detect with certainty small abnormalities in the secretory power of the stomach due to disease.

The trained statistician reviewing a study such as the one we are reporting will always want to know the range of a group of measurements made on one person. In other words, he will want to know the error of the method and the variation in the readings made on one individual day after day. Unfortunately, we cannot as yet give definite information on this point. The few studies reported thus far in the literature are vague, and the conclusions are not in agreement. Our own study designed to answer this question is now under way.

It is perhaps suggestive that duodenal ulcers so often appear in men between the ages of 20 and 25 years, about the time when the strength of the gastric acids is rapidly increasing. It would be more suggestive were it not for the fact that gastric ulcers usually do not make their appearance until the next decade. It may be that the three times greater incidence of ulcer in men than in women is associated with this decided difference in acidity.

There are so few things new under the sun that we do not dare to state that this big difference between the acidity in men and women has not been observed before, what we can say is that the fact was new to us.

SUMMARY

Satisfactory standards of normal gastric acidity have so far been lacking. A study has been made of data from 3,746 persons in whom careful examination did not reveal any disease which could conceivably affect the mucous membrane or the secretory activity of the stomach.

There was a steady increase in the incidence of achlorhydria from youth to old age. At the age of 60 years 28 women in 100 (in our series) failed to show free acid on repeated fractional analysis, and similarly, 23 men in 100 were achlorhydric. In an additional 5 per cent of women and 3 per cent of men there was no free acid in the first sample of an Ewald meal removed at the end of an hour.

Free gastric acidity appears to increase rapidly from childhood up to the age of 20 years when adult values are reached. About the age of puberty, the average value for boys begins to rise considerably above that for girls.

In order to simplify the statistical study of the group of persons with free acid all data from persons with true or apparent achlorhydria were first removed from consideration.

We can now say that modal free acidity for men ranges between 45 and 50 units in the years from 20 to 40. After this it falls off rapidly to a level of from 30 to 35 units in the aged. The mode for women is approximately 35 units throughout adult life. It appears to fall off slightly after the age of 60 years. The normal range of free acidity in both men and women is about 90 units.

Chart 4 shows that the modal total acidity for women is practically constant at a level of about 51 units between the ages of 20 and 60 years; the mode for men ranges from 66 at the age of 20 years down to 56 after the age of 65 years. For both free and total acidity, mean and modal values were about the same.

In both sexes the combined acidity appears to vary but little from youth to old age. Ninety per cent of the data lay between limits of 12 and 22 units with a mode at 17 units.

The data suggest that the process which gives rise to achlorhydria is not the same as the one that in men after 40 years produces a gradual falling off in acidity. The absence of such a gradual decrease in the older women makes it seem improbable that in either sex there is a progressive senile atrophy of the gastric mucosa.

THE SYSTEMIC EFFECTS OF HISTAMINE IN MAN
WITH SPECIAL REFERENCE TO THE RESPONSES OF THE
CARDIOVASCULAR SYSTEM ^k

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The concept that histamine plays a fundamental rôle in the chemical control of the circulation is suggested by a series of observations by Dale and Lewis and their associates¹ It is, however, remarkable that the evidence concerning histamine as a vasodilator substance in the physiologic regulation of the circulation is still largely based on indirect evidence and analogical observations Direct proof for this function of histamine in the animal body is so far not available, and while the value of parallel and "teleologic evidence" in establishing a physiologic concept is considerable, it is recognized that concepts based on indirect evidence may be open to fallacy and therefore cannot be considered as proved

Burn and Dale and their associates² observed a fall in the arterial blood pressure in anesthetized carnivorous animals Lewis and his associates³ presented evidence that the human skin, when subjected to various sorts of stimuli, reacts in the same manner as it does after intracutaneous puncture with small amounts of histamine They claimed that the vasodilatation of the minute vessels of the skin follow-

¹ Submitted for publication, May 5, 1931

² From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine of Harvard Medical School

³ Barger, G, and Dale, H H The Presence in Ergot and Physiological Activity of B-Imidazolylethylamine, *J Physiol* **40** 38, 1910 Dale, H H, and Laidlaw, P P The Physiological Action of B-Imidazolylethylamine, *J Physiol* **41** 318, 1910 Dale, H H, and Richards, A N The Vasodilator Action of Histamine and of Some Other Substances, *J Physiol* **52** 110, 1918 Dale, H H, and Laidlaw, P P Histamine Shock, *J Physiol* **52** 355, 1919 Lewis, T The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927

² Burn, J H, and Dale, H H The Vasodilator Action of Histamine, and Its Physiological Significance, *J Physiol* **61** 185, 1926

³ Lewis (footnote 1)

ing these stimuli is due to a substance or substances closely related to histamine. The implication of these observations is that Lewis' H-substance, or histamine, preexists in the cutaneous cells, and is liberated to exert its physiologic rôle only in response to certain stimuli. Best, Dale, Dudley and Thorpe⁴ and Thorpe⁵ demonstrated that when tissues are extracted by a relatively simple chemical procedure, appreciable or large amounts of histamine are obtained. The extract of the lung was found to contain from about ten to twenty times more histamine than the majority of the organs tested, 1 Kg of fresh lung tissue yielding as much as 75 mg of histamine. It is also significant that, according to Dale,⁶ the vasodilator effect of various organ extracts used therapeutically depends entirely on their combined histamine and choline content. Dale and Laidlaw⁷ observed that anesthetized cats, following the sudden and continuous injection of histamine, exhibit a condition resembling in many respects traumatic and surgical shock in man. Cannon⁸ produced evidence that some chemical substance, probably histamine or a substance related thereto, is actually responsible for the manifestations of traumatic shock.

All these observations strongly suggest, then, the active rôle of histamine in the regulation of the normal and abnormal circulation. There are, however, numerous studies reported in the literature that contradict this concept of the physiologic rôle of histamine. Contrary to the behavior of epinephrine, histamine produces varying effects on the vascular system and the minute vessels of different species of animals. Furthermore, the same species of animals may behave differently under diverse conditions.

Histamine produces a fall in the blood pressure of carnivorous animals, and an elevation in rodents. Feldberg's observations in Dale's laboratory⁹ suggest that these variations in the effect of histamine on the blood vessels of different species of animals are more apparent than real, as the effect depends on the tone of the vessels rather than on the species. The evidence presented by Feldberg in support of this

4 Best, C. H., Dale, H. H., Dudley, H. W., and Thorpe, W. V. The Nature of the Vaso-Dilator Constituents of Certain Tissue Extracts, *J. Physiol.* **62** 397, 1927.

5 Thorpe, W. V. Vasodilator Constituents of Tissue Extracts. Isolation of Histamine from Muscle, *Biochem. J.* **22** 94, 1928.

6 Dale, H. H. Some Chemical Factors in the Control of the Circulation, *Lancet* **1** 1233, 1929.

7 Dale and Laidlaw (footnote 1, fourth reference).

8 Cannon, W. B. Discussion sur le choc traumatique, *Mem. Soc. de biol.* **81** 854, 1918, The Course of Events in Secondary Wound Shock, *J. A. M. A.* **73** 174 (July 19) 1919, Traumatic Shocks, Surgical Monographs, New York, D. Appleton & Company, 1923.

9 Feldberg, W. The Action of Histamine on the Blood Vessels of the Rabbit, *J. Physiol.* **63** 211, 1927.

conception is not conclusive however, and thus the "histamine paradox" must be considered unsettled. Burn and Dale² explained the difference in the behavior of animals by the variation of the level at which the constrictor effect of histamine on the central portion of the vascular tree changes to a dilator effect on the peripheral portion. In the dog, for example, the constrictor effect of histamine on the arterial tree changes to a dilator effect at the level of the small visible arteries. In the cat, there is a constrictor effect to the level of the arterioles and capillaries, which, under certain conditions, dilate in response to histamine. In rodents the appearance of the constrictor effect is pushed to the periphery.

It is rather significant that Grant and Jones¹⁰ found that the minute vessels of the skin and mucous membranes of the tongue of the frog respond similarly to those of man with dilatation of the small blood vessels under local stimulus and yet that histamine produces no dilatation of the blood vessels when applied either locally or systemically although histamine has been extracted from the skin of the frog. It is rather difficult to reconcile these variations in vascular response produced by a substance that is supposed to play a uniform regulatory role in the circulation. There is, furthermore, a significant discrepancy between the short duration of action of histamine on entering the blood stream and the relatively long duration of certain vasodilator responses attributed to histamine. Here again, assumptions have been made that histamine or allied substances may be combined with colloids or other substances that alter its persistence of action. Experimental proof for such a statement again is not available.

A considerable gap also exists between the finding of as much as 75 mg per kilogram of histamine in fresh lung tissue and the opinion of Dale⁶ that histamine has "evidently as good a claim to be regarded as a normal constituent of the living cell, as has any other substance which similarly conservative methods could extract." If such small amounts of histamine as 0.1 mg produce profound changes in the minute blood vessels in man, it is difficult to realize how an amount that is many times that of the fatal dose can be attached to the endothelial system of the lungs without exerting any influence on the pulmonary capillaries. Not only is the significance of these apparently contradictory observations obscure, but the interpretation of the observations on the same species is not agreed on (Mautner and Pick¹¹).

10 Grant, R. T., and Jones, T. D. The Effect of Histamine and of Local Injury on the Blood Vessels of the Frog. A Vasodilator Substance in Extracts of Frog's Skin. *Heart* **14** 337, 1929.

11 Mautner, H., and Pick, E. P. Ueber die durch "Shockgifte" erzeugten Zirkulationsstörungen, München med. Wchnschr. **62** 1141, 1915, II. Das Verhalten der überlebenden Leber, *Biochem. Ztschr.* **127** 72, 1922.

The considerations outlined strongly suggest how hazardous it is to define the rôle of histamine in health or in disease from animal observations. The necessity of obtaining direct information from studies on man is obviously great. The study presented here deals mainly with the systemic effect of histamine in human beings. It is fully appreciated that the results of these observations do not necessarily apply to the alleged regulatory functions of histamine between cell and local capillary blood supply where the physiologic relationship is different. The inquiry was centered rather on the influence of histamine on the circulation, metabolism and respiration, as these three functions are closely interrelated, and adjustments in one often produce changes in the others. The response of other bodily functions to histamine was also studied. Whenever possible, quantitative observations were made. The procedures followed in the observations will be described under the proper headings. Although, for clarity, the results obtained are presented in groups, actually, numerous bodily functions were studied simultaneously in the same subject. Simultaneous observations are a safeguard against faulty conclusions and aid considerably in interpreting correctly the interrelations between bodily functions.

In our experience, histamine has been found to have no effect on the cardiovascular system when given orally to man. Several hundred times the fatal intravenous dose, given by mouth, failed to produce appreciable signs or symptoms. On the other hand, histamine is absorbed promptly from the subcutaneous depot, although individual variation in its speed of absorption complicates studies in which comparative quantitative observations are desired. Furthermore, the amount of histamine entering the blood stream from the subcutaneous tissues varies considerably at different time intervals. In order to avoid these variations, the intravenous channel of administration was adopted in a majority of the observations. The effects of both a single intravenous injection and of continuous intravenous infusion were studied. The intravenous method of administration makes the results obtained on different subjects comparable, and since the amount of histamine entering the blood stream in a given unit of time is known, and the persistence of action of histamine, as will be shown, is presumably of short duration, a quantitative relationship can be established between the concentration of histamine in the blood stream and the degree of changes in bodily functions.

Throughout the course of this study, histamine phosphate was used. All figures of "histamine" express amounts of histamine phosphate unless specifically characterized as "histamine base."¹²

¹² The molecular weight of histamine phosphate is approximately thrice that of histamine base.

THE EFFECTS OF THE RAPID INTRAVENOUS ADMINISTRATION
OF SINGLE DOSES OF HISTAMINE

As described in a previous communication¹³ and also reported by others,¹⁴ the sudden single intravenous injection of histamine is followed by a sensation of warmth over the face associated with intense flushing. Depending on the dose administered, the flush may spread to various skin areas toward the feet. There may also be a throbbing sensation over the head with or without headache. Following toxic doses, nausea and vomiting may develop. The heart rate shows an elevation.

Observations on more than a hundred subjects with a normal cardiovascular system established the minimal single dose, just sufficient to produce detectable changes in the minute vessels of the face or an elevation in the cardiac rate, as varying between from 0.01 to 0.03 mg, corresponding to from 0.00015 to 0.0005 mg per kilogram of body weight. A tenfold increase of these minimal amounts occasionally may produce toxic manifestations. In the majority of instances amounts of 0.07 mg or 0.001 mg per kilogram of body weight were administered in a solution of 1:10,000 concentration.

Changes in the Normal Complexes of the Electrocardiogram—In order to ascertain the possible direct effect of histamine on the coronary circulation or the cardiac musculature, continuous electrocardiographic tracings of lead II were taken following the injection of from 0.05 to 0.08 mg of histamine into fifteen subjects with a normal cardiovascular system. The onset of the peripheral vascular responses due to histamine was registered by the electrocardiographic tracings through instantaneous temporary short-circuiting of the galvanometer. Analysis of the records thus obtained indicated that the onset of the acceleration occurs simultaneously or from two to three seconds before the onset of the peripheral vascular responses. Simultaneously with this acceleration the T wave shows a progressive depression. With the return of the normal cardiac rate, the T wave assumes its original shape. Figure 1 represents a typical observation. These changes in the T wave, interpreted in the light of present knowledge, indicate that histamine induces a change in the coronary blood vessels or the musculature. The more exact mechanism or nature of this effect is not clear at present.

13 Weiss, S., Robb, G. P. and Blumgart, H. L. The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, *Am Heart J* 4:664, 1929.

14 Eppinger, H. Ueber eine eigentümliche Hautreaktion hervorgerufen durch Ergamin. *Wien med Wchnschr* 63:1414, 1913. Harmer, I., and Harris, K. E. Observations on the Vascular Reactions in Man in Response to Histamine, *Heart* 13:381, 1926.

Heart Rate and Arterial Blood Pressure—Following the administration of an average dose of 0.001 mg of histamine per kilogram, an elevation in the cardiac rate regularly appears after an interval of from fifteen to twenty-five seconds, corresponding to the circulation time. The maximal average elevation is 15 heart beats per minute, and this usually occurs within one minute after the injection. In a number of instances the maximal rise in the heart rate was from 30 to 40 beats

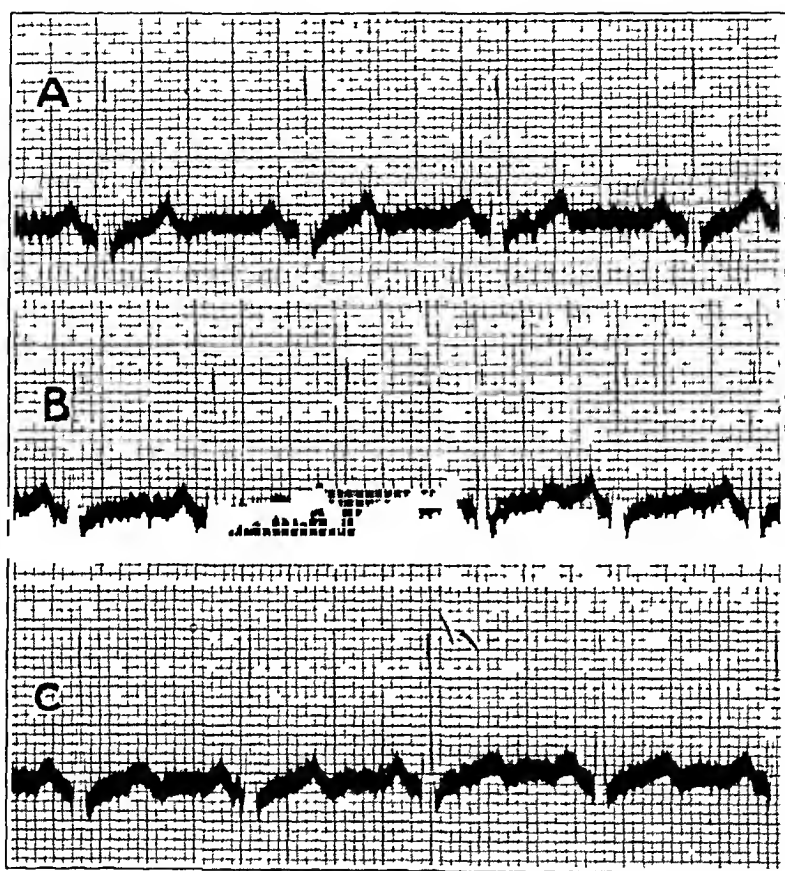


Fig 1—The effect of the sudden intravenous injection of 0.05 mg of histamine phosphate on the normal complexes of the electrocardiogram. A indicates a control tracing, B, a tracing thirty seconds after the injection, note the increase in rate and the depressed T wave, C, a tracing fifty seconds after the injection, the T wave is approaching its normal shape. All tracings are of lead II.

With this elevation of the heart rate, moderate changes in the arterial blood pressure occasionally developed. No change, or a rise of as much as 15 mm of mercury in the systolic and diastolic blood pressures, occurred in the majority of instances (forty-two subjects). A fall of similar order was observed in a small group (eight subjects). The duration of the flush and changes in the cardiac rate and arterial blood pressure lasted from two to five minutes.

Venous Pressure—The venous pressure, as measured continuously by the method of Moritz and Tabora,¹⁵ showed no appreciable changes. Occasionally there was a rise corresponding to 1 or 3 cm of water in the venous pressure. Table 1 presents a few of the observations on the effect of a single dose of histamine on the arterial and the venous pressures.

The Response of the Cerebral and Facial Blood Vessels—Lewis has shown that the minute vessels of the face are especially sensitive to histamine. Our observations indicate that the minute vessels of the brain of man also react to small amounts of histamine. Following the administration of an average single dose of histamine, after an elapse of a period corresponding to the circulation time between the site of the injection and the brain,¹³ there is a prompt rise in the intra-

TABLE 1—*The Effect of a Single Intravenous Injection of Histamine on the Arterial and Venous Blood Pressure*

Observation	Histamine Injected Into Vein, Mg	Histamine per Kg Injected Into Vein, Mg	Circulation Time, Sec	Vital Capacity per Sq Meter of Body Surface, Ce	Arterial Blood Pressure				Venous Blood Pressure	
					Systole		Diastole		Before, Ce H ₂ O	After Ce H ₂ O
					Before, Mm Hg	After, Mm Hg	Before, Mm Hg	After, Mm Hg		
1	0.06	0.001	22	2,400	140 148	140 142	86 92	80 92	6 7	6 7
2	0.07	0.001	32	2,100	164 172	163 174	44 46	48 53	1 2	1 3
3	0.06	0.001	22	2,450	110 112	108 114	70	65 72	4 5	4 7
4	0.08	0.001	20	2,700	135 138	130 137	85	80 85	3	3 4
5	0.08	0.001	25	2,400	125 120	115 125	60 70	58 70	3 4	3 5
6	0.07	0.001	18	2,100	110 120	110 125	65-80	60 80	1 2	1 2
7	0.08	0.001	20	2,500	126 132	118 135	70 75	70 80	6 7	5 7

cranial pressure, as indicated by the changes in the fluid level of the manometer connected with the subarachnoidal space. Simultaneously with the onset of this rise in the pressure of the cerebrospinal fluid, the cardiac pulsatile expansion of the spinal fluid increases to three or four times normal. This usually lasts several minutes after the return of the cerebrospinal fluid to its initial level (table 2). In observations in which the arterial and venous pressures were measured simultaneously with the cerebrospinal pressure, it was found that the rise in the spinal pressure as well as the increase in the pulsatile expansion of the spinal fluid, may occur without necessary alteration either in the arterial or in the venous pressure.

Such a rise in the spinal pressure with increased pulsatile expansion and without simultaneous change in the arterial and venous pressure can be attributed only to a dilatation of the arterioles, capillaries and venules which results in an increase in the volume of blood in the brain.

15 Moritz F and Tabora D V. Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exact zu bestimmen, *Deutsches Arch f klin Med* 98:475, 1910.

That this inference is indeed correct has been substantiated by direct observation of the effect of histamine on minute vessels of the brain. In cases in which the brain surface was exposed for removal of a neoplasm, the intravenous administration of from 0.05 to 0.1 mg of histamine was followed by a prompt expansion of the brain volume associated with a marked increase in the cerebral pulsation and the appearance of a bright flush. These changes lasted for from ninety to one hundred and twenty seconds.

The following case gives a summary of one of these observations.

A McE, aged 21, was operated on for the removal of an intracranial neoplasm. Ether anesthesia was used. A large round area of the skull over the right temporo-parietal area was removed, and the dura was opened. The exposed brain area was clear. The heart rate was 76 per minute, the arterial systolic blood pressure was

TABLE 2—*The Effect of Histamine on the Intracranial Pressure*

Observation	Histamine Injected Into Vein, Mg	Histamine per Kg, Mg	Arm—Face Circulation Time, Sec	Arm—Brain Circulation Time, Sec	Intracranial Pressure Maximum		Maximum Elevation, Mm H ₂ O	Duration of Rise, Sec
					Before, Mm H ₂ O	After, Mm H ₂ O		
1	0.07	0.001	13	12	140	250	110	90
2	0.05	0.001	14 15	15	140	290	150	105
3	0.07	0.001	17	16	110	280	170	90
4	0.06	0.001	16	17	100	300	200	75
5	0.02	0.0005	19	17	175	290	115	80
6	0.08	0.001	19	19	230	350	120	100
7	0.10	0.002	19	20	185	250	65	80
8	0.08	0.001	21	22	75	200	125	

100 mm of mercury, the diastolic pressure, 50 mm. Nine-hundredths milligram of histamine phosphate in a solution of 1:5,000 was injected into the foot vein. Fourteen seconds later a distinct increase of the pulsation of the brain was noted, and simultaneously there were an appreciable swelling and bulging. The surface of the brain became pink, and even the small visible vessels (presumably veins) became engorged. The cardiac rate rose to a maximum of 82 beats per minute. These changes reached their maximum in from thirty to thirty-five seconds after the onset and disappeared in three minutes. There was no appreciable change in the arterial blood pressure. Five minutes later 0.1 mg of histamine was again injected into the foot vein with an identical effect.

That the arterioles and other minute vessels of the human brain respond with dilatation to histamine was further substantiated by a third set of observations in which the oxygen difference between the arterial blood and the venous blood obtained from the internal jugular vein was studied before and after the administration of histamine.¹⁶

16 Weiss, S., Lennox, W. G., and Robb, G. P. The Dilator Effect of Histamine on the Cerebral Vessels in Man, *Proc. Soc. Exper. Biol. & Med.* **26**: 706, 1929. Weiss, S., and Lennox, W. G. The Cerebral Circulation. XVII. Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, *Arch. Neurol. & Psychiat.* **26**: 737 (Oct.) 1931.

The vessels of the eyeground failed to reveal obvious changes following the administration of histamine

The observations presented establish the fact that the arterioles and the minute vessels of the brain respond with dilatation following the intravenous administration of histamine. In order to establish a quantitative index as to the relative sensitivity of the cerebral blood vessels, the minimal effective dose that produced dilatation in the cerebral vessels as indicated by the rise in cerebrospinal pressure and an increase in pulsatile movements was compared with the minimal dose that produced a flush in four subjects in whom puncture of the subarachnoid space was performed for therapeutic purposes. Table 3 presents the results of a few of these observations. In the instances presented, although the minimal dose (table 3) failed to produce changes

TABLE 3—*The Relative Sensitivity of the Cerebral Blood Vessels to Histamine, as Compared with That of the Facial Vessels*

Observation	Histamine Injected Into Vein Mg	Histamine per Kg, Mg	Onset of Flush, Sec	Onset of Rise in Intracranial Pressure, Sec	Maximum Intracranial Pressure After Histamine, Mm H ₂ O		Maximum Rise by Histamine, Mm H ₂ O	Duration of Rise in Intracranial Pressure, Sec
					Before	After		
1	0.02	0.0003		16	120	180	60	120
	0.04	0.0006	17	16	110	250	140	115
	0.07	0.0010	17	17	125	300	175	130
2	0.005	0.0001		17	170	230	50	80
	0.025	0.0006	19	17	175	290	115	80
3	0.02	0.0002		24	150	350	200	100
	0.03	0.0003	26	24	190	450	300	110
4	0.01	0.0002		26	65	110	55	130
	0.03	0.0006	26	26	40	100	60	120

in the facial vessels there was a response in the cerebral vessels as indicated by both the elevated intracranial pressure and the increase in the pulsatile expansions. It would appear, then, that the sensitivity of minute blood vessels of the human brain to histamine is unusually great, probably greater even than that of the minute vessels of the face which has been considered the vascular area most sensitive to histamine.

Cutaneous Blood Flow of the Face—As the flush is most intense over the face the change of the blood flow in this area following the appearance of the flush was measured by determining the skin temperature with the aid of a thermocouple connected with a calibrated galvanometer.¹⁷ In one group of subjects, with the development of a bright red flush there was a rise in the skin temperature of as much as 2.5 C (36.5 F) indicating an increase in the blood flow. In another group such changes were not observed. The latter group tended to develop a cyanotic flush.

¹⁷ Benedict F. G. Die Temperatur der menschlichen Haut, *Ergebn d Physiol* 24: 594, 1925.

Blood Flow Through the Capillaries of the Finger-Nail Bed—With the aid of a special microscope, repeated observations were made on the shape of the capillaries of the finger-nail bed and on the blood flow through them after the injection of from 0.02 to 0.1 mg of histamine. Such amounts of histamine induced no flush over the fingers. No changes in the shape of the capillaries was noted. Coinciding with the onset of the flush over the face, there was an increase in the velocity of the blood flow.

THE EFFECTS OF THE CONTINUOUS INTRAVENOUS ADMINISTRATION OF HISTAMINE IN MAN

In studying the effect of the continuous intravenous administration of histamine, solutions of various concentrations, from 1:100,000 to 1:5,000, were employed. Histamine phosphate was dissolved in sterile physiologic solution of sodium chloride, the concentration of which, as determined by its freezing point, was 0.89 per cent. A special arrangement permitted continuous uniform infusion of the desired amount of histamine. It was also possible to change from one concentration of solution to another or to a physiologic solution of sodium chloride. An infusion of saline, as a control solution, preceded each administration of histamine.

The subjective sensations following the continuous infusion of histamine are essentially those experienced after the injection of a subcutaneous or a single intravenous dose. A sensation of heat over the face, fulness over the head and slight palpitation follow infusion of minimal effective amounts. Increase in the rate of injection is associated with fulness of the head, a pulsating headache, palpitation, perspiration, nausea and vomiting. Headaches occur less often and with less severity providing the rate of injection is increased gradually, when relatively large continuous doses are given than after the injection of a single dose. It appears that sudden change in concentration plays an important rôle in precipitating headaches. It seems especially significant that, regardless of the duration of the infusion, the intensity of the symptoms remains essentially unchanged as long as the rate of injection is unaltered. Often the symptoms become less severe with the progress of time.

The Susceptibility of Man to Histamine—The minimal effective dose manifests itself in a slight elevation of the cardiac rate and in dilatation of the minute vessels of the face. If a subminimal dose is infused, such responses are not observed even when the same rate is maintained for hours. If histamine is infused at a rate greater than that of the minimal dose, a response of the cardiovascular system follows, the intensity of which depends entirely on the rate

but not on the duration of the injection. These observations clearly demonstrate that histamine is changed to a pharmacologically ineffective substance or substances practically as fast as it is infused into the human circulation. For this reason, by determining the rate of injection of a subminimal and a minimal effective rate, one can estimate the susceptibility of the cardiovascular system of man to histamine. Furthermore, because the response of the minute cutaneous blood vessels and the cardiac rate occurs earlier than the other bodily reactions, the minimal dose represents the sensitivity of man to hista-

TABLE 4—*The Minimal Dose of Histamine Effective in Man*

Observation	Age	Histamine, Mg per Min	Concentration of Histamine Injected	Histamine, Mg per Kg per Min	Heart Rate per Min	Arterial Blood Pressure		Response of Facial Vessels
						Systolic, Mm Hg	Diastolic, Mm Hg	
1	35	0.01	1:10,000	0.00018	78	125	80	—
2		0.02	1:10,000	0.00036	96	128	84	+
3	29	0.01	1:50,000	0.00018	80	118	70	—
4		0.02	1:50,000	0.00036	88	122	68	+
5	29	0.01	1:50,000	0.0001	76	112	78	+
6	25	0.006	1:100,000	0.00008	72	128	66	—
7		0.012	1:100,000	0.00015	72	128	60	+
8	24	0.004	1:100,000	0.00006	82	126	76	—
9		0.006	1:100,000	0.00008	82	124	70	+
10	25	0.004	1:100,000	0.00006	60	104	68	—
11		0.01	1:100,000	0.00016	64	104	70	+
12	24	0.005	1:100,000	0.00006	72	110	90	—
13		0.010	1:100,000	0.00012	72	114	94	+
14	2	0.004	1:10,000	0.00007	80	90	60	—
15		0.007	1:10,000	0.00012	80	90	60	+
16	17	0.005	1:10,000	0.00012	66	98	68	—
17		0.007	1:10,000	0.00016	68	98	70	+
18	40	0.006	1:10,000	0.00006	80	138	80	—
19		0.012	1:10,000	0.00012	80	138	78	+
20	62	0.004	1:10,000	0.00008	68	130	68	—
21		0.008	1:10,000	0.00016	70	132	68	+

mine. Such observations permit also the estimation of the minimal effective dose of histamine in the blood stream. Table 4 presents these observations. The minimal effective dose varied from 0.006 to 0.02 mg per minute, with an average rate of 0.01 mg. Although the age of the subjects varied from 17 to 65, the variation in age did not influence the susceptibility of the subjects.

Changes in the Normal Complexes of the Electrocardiograms—The influence of the continuous intravenous administration of histamine on the complexes of the normal electrocardiogram has been studied in the manner described. Progressively larger doses were administered. Analysis of the tracings indicate that histamine in doses as small as 0.004 mg per minute may depress all the complexes of the electrocardiograms. The effect is especially marked on the T wave. The degree of the depression or inversion is to a certain extent propor-

tional to the rate of administration. Figures 2 and 3 represent two of the observations made. Subject G M (fig 2), aged 27 received following a control tracing, progressively increasing amounts of histamine from 0.006 mg per minute to 0.04 mg per minute. The T wave exhibits a progressive depression although even such large amounts as 0.04 mg per minute, corresponding to 2.4 mg per hour, failed to invert the T wave. In the case of subject L M D (fig 3), aged 16 on the other hand, 0.012 mg per minute produced an inversion of the T wave. These changes in the T wave disappeared within a few

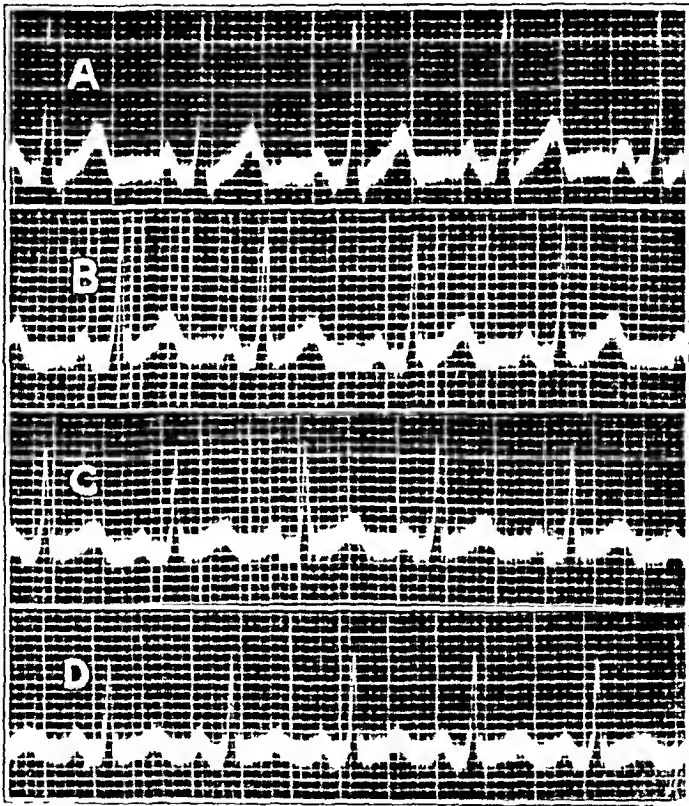


Fig 2—The effect of the continuous intravenous administration of histamine on the complexes of the normal electrocardiogram. *A* indicates a control tracing, *B*, a tracing with an injection rate of 0.01 mg per minute, *C*, a tracing with an injection rate of 0.02 mg per minute, *D*, a tracing with an injection rate of 0.04 mg per minute. Tracings *B*, *C* and *D* show a progressive decrease in the T wave. All tracings are of lead II.

minutes after the infusion of histamine stopped. The results and the interpretations of these observations are identical to those described after the sudden injection of histamine.

Heart Rate and Arterial Blood Pressure—Figure 4 presents the relationship between the dosage of histamine and the cardiac rate. The duration of the infusion at an even rate lasted from fifteen to twenty

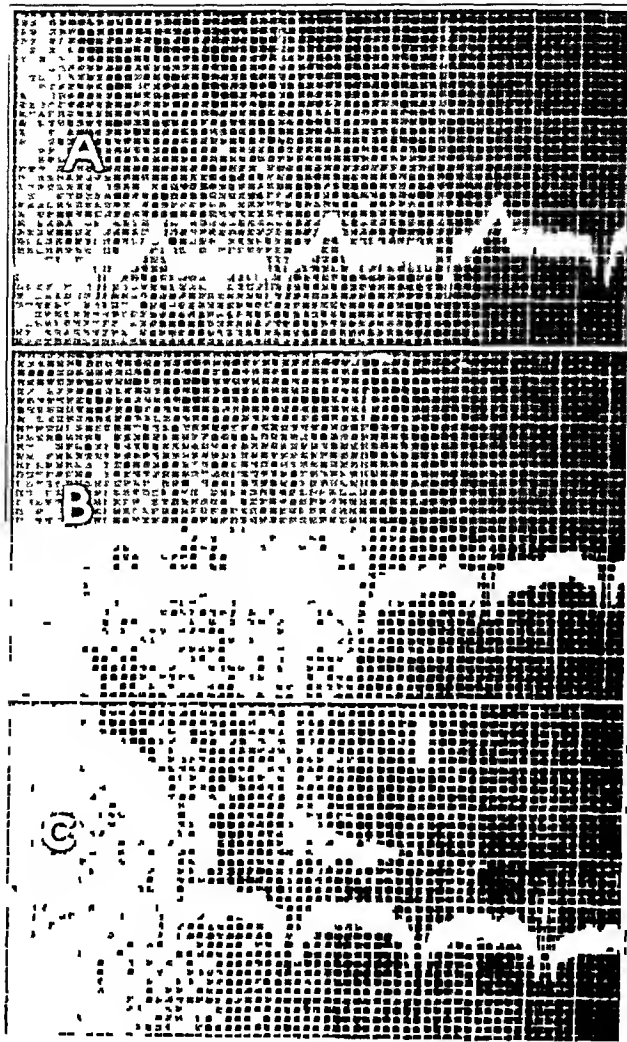


Fig 3—The effect of the continuous intravenous administration of histamine on the complexes of the normal electrocardiogram *A* indicates a control tracing, *B*, a tracing with an injection rate of 0.012 mg per minute, *C*, a tracing with an injection rate of 0.016 mg per minute. In tracings *B* and *C* the T wave is inverted. All tracings are of lead II.

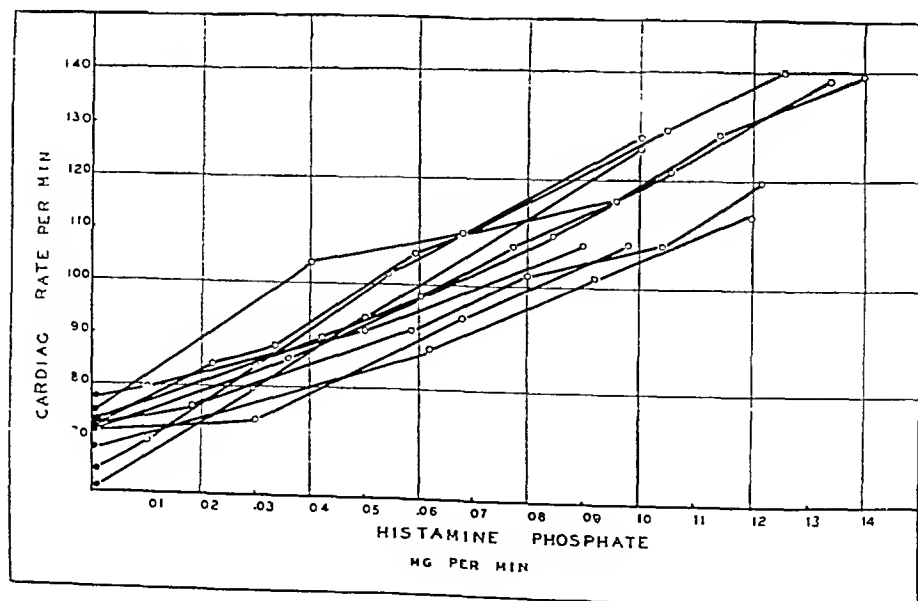


Fig 4—The relationship between the infusion of histamine and the cardiac rate. The dark dots represent the average of the control heart rates before the administration of histamine, the small circles, the average cardiac rate in response to various rates of infusion of histamine, each of which lasted from fifteen to twenty minutes.

minutes. The dots of the curves represent an average of several readings at the same rate of injection. Increasing amounts of histamine were administered to the same subject. The degree of elevation of the cardiac rate was unchanged when the same rate of injection was maintained, although if the rate was maintained for a longer period, such as an hour or two, the cardiac rate gradually became elevated. An increase in the amount injected per minute produced a progressive rise in the cardiac rate. In addition to the observation charted, in a number of instances higher amounts of histamine were infused, up to 0.4 mg per minute. The elevation of the cardiac rate above 120 was relatively slight even when the dose was increased considerably. The maximal rate per minute was observed after the injection of 0.4 mg per minute. The maintenance of this rate of injection for one hour was accompanied by toxic symptoms, which made further increase of rate undesirable. The general behavior of the subject and the cardiovascular system in these observations was not similar to the description of experimental histamine shock.

Intravenous injection of a single dose of histamine as a rule fails to produce a fall in the arterial blood pressure in normal subjects. Because histamine is rapidly destroyed in the human body, it seemed desirable to investigate the effect of continuous injections of histamine on the arterial blood pressure. Observations on certain species of animals seemed to justify the assumption that histamine would also lower the arterial blood pressure of man. This alleged effect certain investigators considered significant in shock and other abnormal states of the body.

The arterial blood pressure was measured by the Riva-Rocci mercury manometer, and in a number of instances was also graphically recorded with the Tycos apparatus. The arterial blood pressure was determined repeatedly on forty subjects with a normal cardiovascular system. In addition, a special study of the blood pressure was made on ten normal subjects to whom progressively increasing doses, as indicated in figures 5 and 6, were administered. The rate of dosage varied from 0.01 to 0.13 mg per minute, and the duration of the injection lasted from fifteen minutes to two hours at each rate of injection. The curves of these ten subjects parallel the findings of the larger unrecorded groups. The systolic blood pressure was essentially unaltered. Some cases tended to show slight elevation, but the average curve of the systolic blood pressure was essentially a horizontal line. The diastolic blood pressure showed no uniform change, its average curve showing a slight tendency to fall as the rate of injection reached 0.08 mg per minute or above. Considering that the injection at such a relatively high rate

as from 0.08 to 0.14 mg per minute is associated with intense systemic reaction and with a marked elevation of the cardiac rate, it was surprising to observe the lack of any uniform lowering of the systolic and diastolic blood pressures

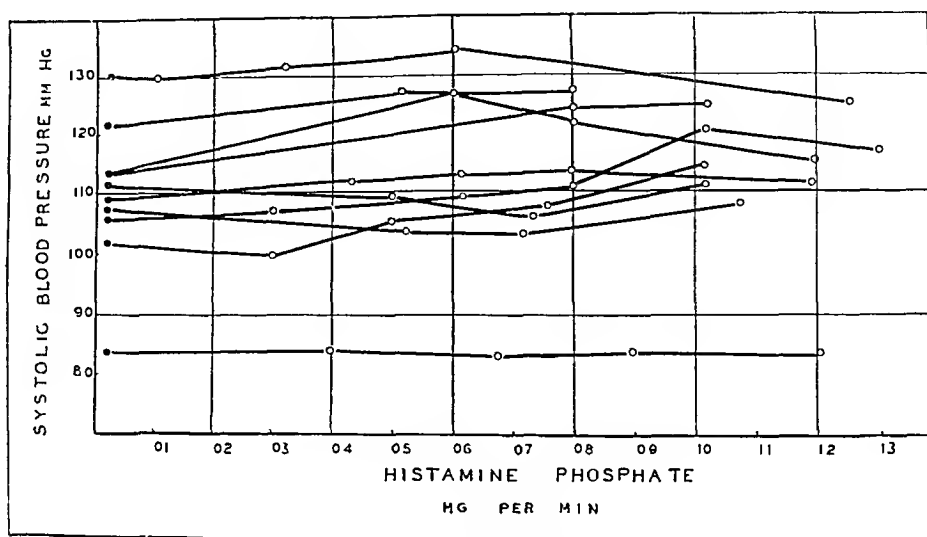


Fig 5—The effect of the continuous intravenous infusion of histamine on the systolic arterial blood pressure

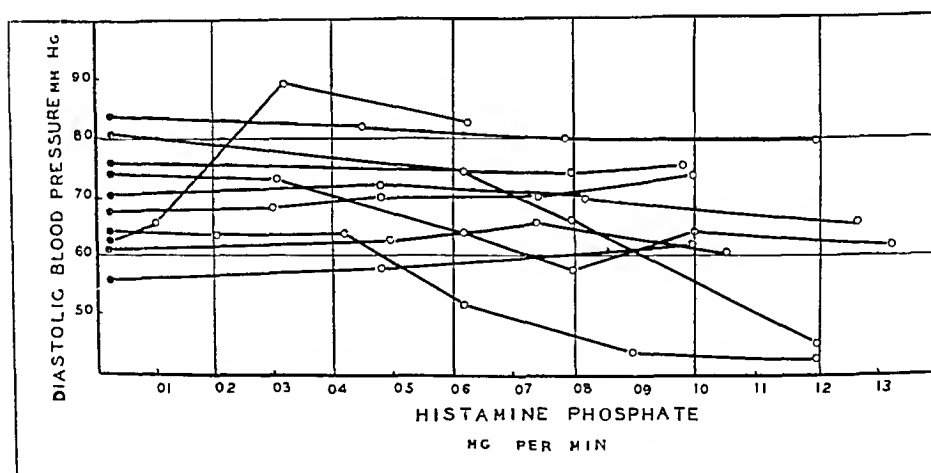


Fig 6—The effect of the continuous intravenous infusion of histamine on the diastolic arterial blood pressure

Venous Pressure—In ten subjects in whom the effect of gradually increased amounts of histamine on the arterial blood pressure and on the cardiac rate were studied additional observations were made on the venous pressure as measured by the Moritz and Tabora method¹⁵ Either no change or a moderate rise which in three instances was 3.5 cm of water was observed. The average venous pressure before

the administration of histamine was 6 cm, during the administration of histamine, 7.4 cm

Capillary Pressure—In five subjects the pressure in the minute vessels of the skin was measured according to the method of Lewis and Haynal¹⁸ at the height of the histamine effect. Both the open and the closed capsules were employed. The results of these measurements showed that the pressure in the minute vessels varied between 10 and 18 mm of mercury, with an average of 16 mm, as contrasted with a variation of from 6 to 12 mm of mercury, with an average of 9 mm, obtained on subjects without the histamine effect. These results indicate but a slight arteriolar dilatation during the height of the histamine effect following the administration of from 0.1 to 0.2 mg per minute, as contrasted with the marked arteriolar dilatation that followed the direct cutaneous puncture of histamine 1:1,000. In a previous communication,¹⁹ it was shown that following such a cutaneous puncture of histamine, the capillary pressure rises to from 40 to 60 mm of mercury, with an average value of 55 mm.

The Response of the Cerebral Vessels—In a group of five subjects on whom spinal puncture was performed for diagnostic purposes, the effect of the continuous intravenous infusion of histamine on the cerebral vessels, when administered in increasing amounts, was studied. Again, the observation was made that minimal amounts of histamine, at a rate of from 0.003 to 0.008 mg per minute, which were insufficient to produce an increase of the heart rate or a dilatation of the cutaneous blood vessels, produced an increase in the pulsatile expansion of the cerebrospinal fluid. This expansion often was not associated with a rise in the spinal pressure. With an increase in the rate of the injection, the degree of pulsation increased, and there was also a rise in the spinal pressure. The height of the increase in the cerebrospinal pressure depended on the amount of histamine injected and on the degree of change from one dose to another. The rise following the injection of 0.1 mg per minute was usually from 150 to 200 mg of water. With the maintenance of the rate for longer than ten minutes, the pressure often returned to normal, but the increased oscillation continued unaltered as long as the injection of histamine continued.

Our interpretation of these observations is that with the administration of histamine there is a dilatation of the minute vessels, resulting

18 Lewis, T, and Haynal, I. Observation Relating to the Tone of the Minute Vessels of the Human Skin. With Remarks upon and Illustrations of Measurements of Pressure Within These Vessels, *Heart* **14** 177, 1928.

19 Ellis, L. B., and Weiss, S. The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation, in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, *J. Clin. Investigation* **8**:47, 1929.

in an increase in the volume of the brain and hence in an increase in the spinal pressure. The increased oscillatory movements, in the absence of changes in arterial and venous pressure, are due to dilatation of the arterioles and perhaps of other minute vessels. If the infusion of histamine is maintained, the elevation in spinal pressure caused by the increased volume of the brain disappears, perhaps because of an increased absorption of the spinal fluid, but the oscillatory movements are unchanged because the arterioles continue to be in a state of relaxation.

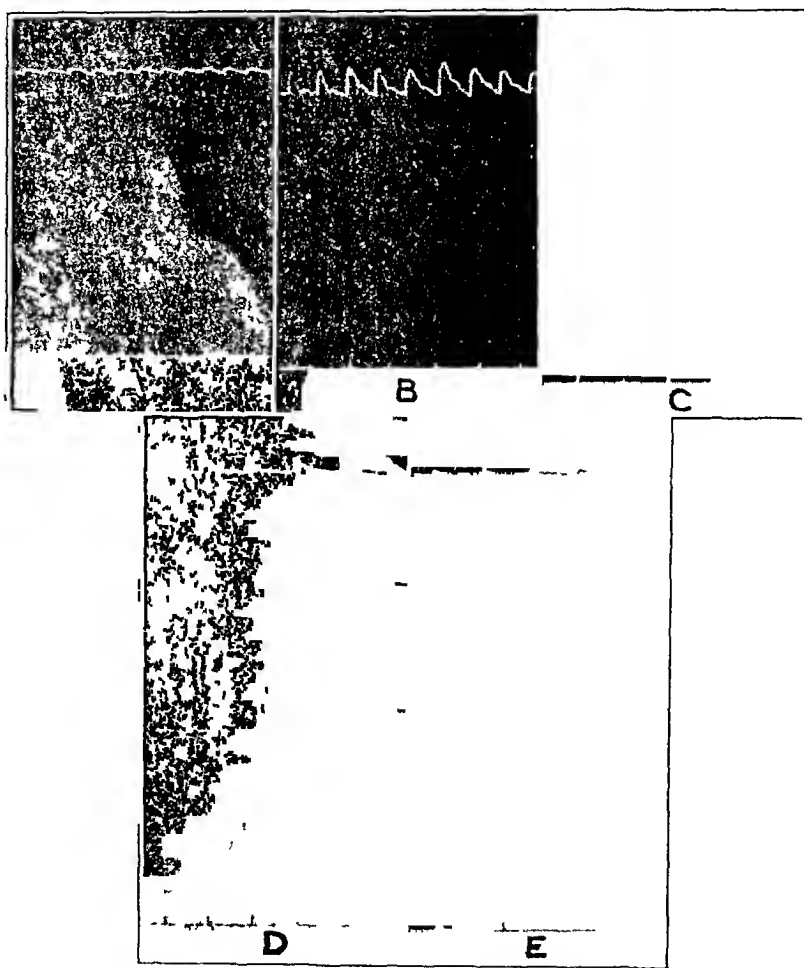


FIG 7—The dilator effect of histamine on the pulsatile expansions of the cerebral blood vessels. *A* indicates a control tracing, *B*, a tracing with an injection rate of 0.02 mg per minute, *C*, a tracing with an injection rate of 0.05 mg per minute, *D*, a tracing three minutes after the injection of histamine was stopped, *E*, a tracing ten minutes after the injection of histamine was stopped.

Another opportunity to demonstrate the effect of histamine on the cerebral blood vessels was given through observations on a patient with a cranial defect as the result of an operation for the removal of a neoplasm. The pulsation of the brain was registered with the aid of a flat, round oncometer applied over the cranial defect. Part of the

results of these observations are given in figure 7. As indicated, immediately after the administration of histamine at a rate of 0.02 mg per minute, there was a marked increase in the pulsatile expansion of the brain. This increase continued as long as the histamine was being infused. With cessation of the histamine, the pulsation returned to normal within ten minutes. The arterial and venous blood pressures remained unaltered during the administration of histamine.

These vascular reactions following the continuous administration of histamine are of the same character as those that follow the injection of a single dose of histamine.

The Response of the Cutaneous Blood Vessels—The flush that follows the administration of histamine is one of its most striking effects. The nature of this reaction was investigated in a long series of experiments. Increasing amounts of histamine were injected into normal subjects, and the change in color of the skin was compared with that of the skin temperature at various standard areas over the face, chest, arms, abdomen and lower extremities. The temperature of the skin was measured with a thermocouple. The room temperature was kept as constant as possible. Even under such experimental conditions, considerable spontaneous fluctuation of the skin temperature was observed in certain subjects. Following several control observations with and without intravenous injection of saline, the administration of histamine was started and the measurements of the skin temperature repeated frequently at from five to ten minute intervals.

The color of the skin depends largely on the state of the subpapillary venules and, to a lesser degree, of the capillary bed.³ A flush, therefore, may be due to a dilatation of the venules alone or to a dilatation of the venules together with the arterioles and capillaries. If there is arteriolar dilatation, the blood flow through the flushed skin area increases, and the degree of increase in blood flow is indicated by an elevation of the skin temperature.

A study of the reaction of the cutaneous blood vessels to histamine in thirty normal subjects indicates that the vascular response is not uniform. As suggested in a previous communication,²⁰ the sensitivity of the minute vessels generally decreased progressively from head to foot. The flush, however, even within the same anatomic area, is not always uniform. In one group of subjects the flush did not proceed downward diffusely with increasing dosage, but the skin areas assumed a mottled appearance with blotchy white islands in the midst of the deep red, flushed areas. The blood vessels within the white areas were apparently relatively resistant to histamine. With elevation of

20 Weiss, S., and Ellis, L. B. The Circulatory Mechanism and Unilateral Edema in Cerebral Hemiplegia, *J. Clin. Investigation* 9: 17, 1930.

the dosage, they often became red. On repeated experiments, the same subject as a rule responded with a mottled flush. In a number of instances, when the same rate of injection was maintained for over an hour, it was observed that the intensity of flush had a tendency to become less and that the mottled white areas gradually increased. These variations in the response of the cutaneous blood vessels may offer an explanation of the individual variations observed in the dermal manifestation of certain diseases.

All the subjects responded with flush, and the appearance of the flush over different skin areas and the dose required to produce it were fairly uniform. However, not all subjects responded with an elevation of the skin temperature. Of the twenty-five subjects, there were six who, even with such large amounts of histamine at 0.2 mg per minute up to the appearance of the toxic manifestation, showed no elevation of the skin temperature, although a deep cyanotic flush developed. In another group of twelve cases, with the appearance of an intense cyanotic flush, there was no elevation of the skin temperature, but with elevation of the dose, the cyanotic tint changed to bright red and an elevation of the skin temperature appeared. After the injection had been stopped, the flush lasted, although the skin temperature returned to normal. In certain of these cases it was also observed that with the same dose one area might show elevation in skin temperature while others did not. This type of reaction occurred most frequently. A third group (seven cases) always responded to histamine with bright color and an immediate elevation of the temperature.

These observations indicate that histamine produces a dilatation of the venules more regularly than of the arterioles. Dilatation of the venules frequently occurs without simultaneous dilatation of the arterioles. Slight dilatation of the arterial loop of the capillaries was observed only with arteriolar dilatation. That histamine has a predilection for the venules and the small veins is also substantiated by observation of the small visible vessels of the conjunctiva. Histamine produced with regularity a diffuse engorgement of the small veins, resulting in congestion. This congestion appeared promptly with the onset of the injection and disappeared within a few minutes after it ceased. In a number of instances the superficial veins of the arm, especially on the side of the injection, became wider while under the effect of histamine.

Cardiac Output—A knowledge of the cardiac output is essential to an evaluation of the state of the circulation. The output of the heart was therefore measured in seven young normal adults before and during the administration of histamine, applying the Fick principle

with the modification described by Field, Bock and Gildea²¹ Although this method gives somewhat high values, it was satisfactory for these measurements, which were undertaken to discover alterations in the minute and stroke volumes of the heart In addition, this procedure gives important information as to the respiratory function of the blood Seven or more alveolar and mixed venous samples were obtained at each determination The metabolism was measured by Tissot's method The amounts of histamine injected during the determination of the cardiac output varied from 0.05 to 0.08 mg per minute, corresponding to from 3 to 5 mg per hour

Following the determination of the cardiac output and other functions of the circulation under basal conditions and during saline infusion, the injection of histamine was started When the effect of histamine reached its height, usually about fifteen minutes after the onset of injection, measurements of the cardiac output and other factors were repeated Table 5 presents the results Figures for heart rate and blood pressure are averages of several measurements With two exceptions, an elevation of the cardiac output occurred The average elevation of the cardiac output during the administration of histamine was 1.5 liters per minute Because of the disproportionate rise in the heart rate there was a tendency for the stroke volume to fall from the average 109 cc before to 95 cc during the histamine injection There was a rise in the basal metabolism, corresponding to the elevation of the cardiac output, to 20 per cent above the basal control observations The relation between the change in the cardiac output and that in the metabolism was similar to that observed in patients with thyrotoxicosis The elevation in the carbon dioxide output was less than the corresponding increase in the oxygen absorption in every instance, so that a fall of the respiratory quotient ensued Considering that the ventilation showed an elevation less than that expected from the elevation of basal metabolism, it would seem that the carbon dioxide, owing to an insufficient increase in ventilation, was not promptly eliminated from the tissues The fall in the respiratory quotient in these relatively short experiments was more apt to be due to physical alterations between ventilation and blood flow than to a change in the metabolized foodstuffs

Circulating Blood Volume—The circulating blood volume of nine subjects was measured by the method of Keith, Rowntree and Geraghty²² before and during the administration of histamine In

21 Field, H, Jr, Bock, A V, Gildea, E F, and Lathrop, F L The Rate of the Circulation of the Blood in Normal Resting Individuals, *J Clin Investigation* **1** 65, 1924

22 Keith, N M, Rowntree, L G, and Geraghty, J T A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16** 547 (Oct) 1915

TABLE 5—The Effect of Continuous Intravenous Administration of Histamine on the Cardiac Output, Respiration and Metabolism

Observation	Age	Histamine per Min., Mg	Heart Rate per Min	Arterial Blood Pressure			Respiratory Minute Volume	Volume of Single Respiration, Cc	Carbon Dioxide Tension			Carbon Dioxide Output per Min., Cc	Cardiac Output per Beat, Cc	Respiratory Quotient	Metabolism, per Cent
				Systolic, Mm Hg	Diastolic, Mm Hg	Mean, Mm Hg			Alveolar, Mm Hg	Virtual, Mm Hg	Venous Difference, Mm Hg				
1	25	0.07	72	100	64		7.0	411	42.4	49.1	6.7	216	7.8	0.875	+4
			95	106	65		7.4	453	42.5	48.4	5.9	224	9.4	0.766	+23
2		0.05	78	118	70		8.0	381	46.4	51.7	5.3	227	10.6	0.832	+12
			97	115	68		9.3	378	45.1	50.4	5.3	229	10.8	0.755	+28
3	19	0.08	46	104	72		4.8	343	43.0	50.8	7.8	161	5.0	0.805	-19
			74	115	65		5.9	368	41.6	47.6	6.0	187	7.7	0.719	+5
4	10	0.08	65	114	80		6.2	476	34.6	45.8	11.2	197	3.9	0.777	+7
			108	116	76		6.9	460	37.5	46.4	8.9	216	5.4	0.750	+30
5	21	0.08	57	130	80		7.2	437	44.7	51.4	6.7	239	9.2	0.850	+3
			80	112	62		8.1	427	43.7	48.8	5.1	248	12.4	0.745	+15
6	22	0.08	72	105	70		4.8	369	40.3	44.9	4.6	147	7.8	0.744	-11
			93	106	64		6.1	468	39.1	45.9	6.5	201	7.4	0.693	+30
7	26	0.07	83	132	86		5.8	413	43.8	51.5	7.7	222	7.0	0.742	+28
			120	129	80		6.2	443	44.3	51.0	6.7	228	8.5	0.737	+33

every case the injection of histamine had been going on for at least an hour in sufficient concentration to give marked systemic effects. The subjects were the same as those in whom the cardiac output was measured. Table 6 presents the results of these observations. The blood volume showed no significant change in five persons, a slight increase in two and a moderate decrease in two. The plasma volume showed no important changes in six subjects, and a slight decrease in three. The hematocrit reading was increased in six, slightly decreased in one and unchanged in two.

Metabolism—In order to ascertain whether or not the described changes in the circulation were associated with changes in the

TABLE 6—*The Effect of Histamine on the Circulating Blood Volume*

Observation	Histamine per Min., Mg	Plasma Volume	Blood Volume	Blood Volume, per Cent of Body Weight	Hematocrit Reading	Comment
1		2,860	5,085	6.58	43.8	Before histamine
2	0.07	2,860	5,432	7.03	47.4	During histamine
3		2,710	5,355	8.33	49.4	Before histamine
4	0.05	2,710	5,370	8.33	49.5	During histamine
5		2,825	4,790	7.50	41.0	Before histamine
6	0.08	2,412	4,246	6.63	43.2	During histamine
7		2,690	4,485	7.60	40.0	Before histamine
8	0.08	2,520	4,295	7.28	41.4	During histamine
9		2,615	4,675	8.22	44.1	Before histamine
10	0.08	2,245	4,075	7.15	45.0	During histamine
11		3,425	6,265	7.55	45.4	Before histamine
12	0.08	3,150	6,100	7.35	48.3	During histamine
13		2,650	4,675	7.87	43.3	Before histamine
14	0.07	2,750	4,850	8.15	43.3	During histamine
15		2,570	4,890	7.43	47.5	Before histamine
16	0.10	2,635	4,845	7.36	45.6	During histamine
17		2,930	5,300	8.22	44.5	Before histamine
18	0.10	2,850	5,625	8.72	48.9	During histamine

metabolism, the oxygen consumption observed under basal conditions was compared with that found during the administration of histamine. Two sets of experiments were devised. In one group of subjects the oxygen consumption was followed with the Benedict Roth instrument. After control measurements with and without the injection of saline, increasing amounts of histamine were infused up to the rate of 0.12 mg. for one hour, and the metabolism was measured repeatedly. Control measurements were also performed after the administration of histamine ceased. In all subjects an elevation of the basal metabolism was found, which returned to the original level after the infusion of histamine was stopped. Control infusions of saline produced no changes. Three of the typical experiments are given in table 7. The rate of elevation varied in some instances, reaching as high as 50 per cent. In another group of seven subjects, presented in table 4, the oxygen and carbon dioxide exchange was measured by the Tissot

method In these cases, again, an elevation was found in every instance With the same rate of injection, considerable variation was shown in the degree of elevation of the metabolism

Effect on the Red Cells and White Cells—In five normal subjects, following the administration of histamine in amounts of from 7 to 10 mg per hour, the effect on the formed elements of the blood was

TABLE 7—*The Effect of Histamine on Oxygen Consumption*

Age	Observation	Heart Rate per Min	Arterial Blood Pressure		Histamine per Min, Mg	Oxygen per Min, Ce	Calories per Hour per Sq M	Metabolism, per Cent of Normal	Comment
			Systolic Mg Hg	Diastolic Mg Hg					
19	1	68	116	58		271	36.2	-12	Control with saline infusion
	2	69	114	60	0.04	272	36.5	-11	
	3	82	110	76	0.08	314	42.1	+2.5	
	4	60	112	78		270	36.3	-11	Ten minutes after injection of histamine stopped
28	5	71	104	74		175	33.3	-16	Control without intravenous infusion
	6	71	106	72		165	31.7	-20	Control with saline infusion
	7	90	106	56	0.06	243	46.7	+18	
	8	107	95	50	0.10	341	65.0	+65	
	9	103	110	70	0.10	231	44.4	+11	
	10	86	114	80		208	40.1	+2	Immediately after injection of histamine stopped
	11	84	96	72		206	39.6	0	Five minutes after injection of histamine stopped
	12	80	100	74		177	34.0	-14	Fifteen minutes after injection of histamine stopped
40	13	68	116	86		256	37.4	-3	Control without intravenous infusion
	14	68	112	84		262	41.3	+7	Control with saline infusion
	15	73	110	80	0.01	260	38.2	-1	
	16	92	128	76	0.06	299	43.7	+14	
	17	104	116	45	0.12	378	55.3	+43	
	18	106	116	50	0.12	408	59.6	+55	
	19	72	108	74		271	39.7	+3	Ten minutes after injection of histamine stopped
	20	66	112	84		278	40.7	+6	Twenty minutes after injection of histamine stopped

studied Blood specimens obtained immediately before and ten minutes and one hour after the injections of histamine were started were compared The number of the red and white cells was counted Blood smears for changes in the morphology of the red cells and white cells were studied No definite alterations in the cells and the platelets were observed The red cells, reticulocyte counts and hemoglobin content showed no changes The number of white cells increased in all cases during the administration of histamine The number of the polymorphonuclear leukocytes increased, and the lymphocytes decreased in four of five cases The fifth case had a high monocyte

TABLE 8—*The Effect of Histamine on Certain Chemical Constituents and Physical Characteristics of the Blood*

Histamine per Hour, Mg	Dextrose			Nonprotein Nitrogen			Sodium Chloride			Freezing Point			Protein			Specific Gravity		
	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference
1	6	97	113	32	30	-2	587	603	+13	0.583	0.579	-0.004	6.79	6.60	-0.19	1.0263	1.0255	-0.0008
2	6	87	99	24	24	0	590	590	0	0.567	0.573	+0.011	6.77	6.58	-0.19	1.0257	1.0252	-0.0005
3	7	107	127	31	31	0	587	572	-15	0.562	0.605	+0.043	6.97	7.34	+0.37	1.0270	1.0275	+0.0005
4	7	101	123	31	29	-2	580	598	+ 9	0.575	0.577	+0.002	7.28	7.03	-0.25	1.0268	1.0261	-0.0007
5	8	83	86	21	20	-1	595	594	- 1	0.562	0.543	-0.019	6.20	6.20	0.00	1.0249	1.0248	-0.0001
6	12	83	94	23	23	0	580	573	- 7	0.563	0.551	-0.012	7.19	7.10	-0.09	1.0261	1.0261	-0.0000

* All values, with the exception of the specific gravity and freezing point, indicate the contents in 100 cc of blood

count throughout. There was some increase in the platelet count, and the venous blood obtained during the administration of histamine showed many clumps of platelets. Because of the small number of cases studied and the lack of definite changes, we refrain from drawing conclusions from these observations.

The Chemical Constituents of the Blood—Because of the alleged rôle of histamine in surgical shock, in which condition appreciable concentration of the blood occurs, a number of constituents and characteristics of the blood such as the dextrose, nonprotein nitrogen, sodium chloride, protein, freezing point and specific gravity were measured in six subjects before and after the administration of histamine for one or two hours at a rate of from 5 to 12 mg per hour.

Although the effect of histamine was manifested in all of these cases by rapid heart rate, intense scarlet flush, nausea and severe headache,

TABLE 9—*The Effect of the Continuous Infusion of Histamine on the Lactic Acid Content of Blood*

Experiment	Age	Histamine, Mg per Hour	Effect of Histamine Infusion on Lactic Acid, Mg per 100 Cc			Source of Blood
			Control	After 10 Min	After 60 Min	
1	52	8	11.6	11.0	10.8	Femoral vein
2	50	7	14.0	16.4	11.6	Cubital vein
3	30	7	26.3	20.1	25.2	Cubital vein
4		10	14.1	17.0	17.7	Cubital vein
5	20	7	16.5	15.5	14.2	Cubital vein

as indicated in table 8, no appreciable change in the blood constituents could be detected. The average amount of saline solution injected was 30 cc per hour. The freezing point of the salt solution used varied between Δ 564 and 568. It is hardly probable that the addition of this amount of saline through a relatively long time exerted a significant diluting effect on the blood and hence obscured the changes produced by histamine.

In another five subjects, the influence of histamine on the lactic acid content of the blood was investigated²³. Histamine was administered for one hour, and the lactic acid content was measured as indicated in table 9, before and ten and sixty minutes after the injection of histamine was started. The results of these measurements indicate that the administration of histamine fails to influence definitely the lactic acid content of the blood.

Although measurements of the constituents described failed to indicate any increased concentration of the blood, the average oxygen capacity of the arterial blood in seven subjects in whom the blood

²³ Friedemann, T. E., Cotomo, M., and Shaffer, P. A. The Determination of Lactic Acid, *J. Biol. Chem.* **73**: 335, 1927.

gases were studied rose from 22.1 per cent by volume to 23.7 per cent by volume. The degree of rise was similar in every case. The details of these observations will be reported elsewhere.

Respiration—It was observed previously¹³ that attacks may be precipitated in patients subject to bronchial and cardiac asthma by the administration of small amounts of histamine. Associated with this reaction, there is a reduction of vital capacity, and this, together with a lowered position of the diaphragm and the appearance of bronchi, suggests bronchial constriction. This assumption is further substantiated by the observation that epinephrine promptly relieves asthmatic attacks precipitated by histamine.

This behavior of patients with bronchial and cardiac asthma raises the significant problem as to whether normal persons respond with a similar respiratory embarrassment of lesser degree, or whether in asthmatic patients one is dealing with an altered reaction to histamine. The vital capacity of ten normal subjects was measured before and during the height of the histamine reaction. No change was observed. Graphic representation of the respiration also failed to show change in the rate or depth of the respiration, even when such large amounts as 10 mg of histamine were administered per hour. These findings, together with the comparative respiratory minute volume studies included in table 4 and the lack of changes in the respiratory breath sounds and any complaints of dyspnea in normal persons, indicate that up to toxic doses histamine in normal persons fails to produce bronchial constriction or any other type of respiratory embarrassment. These observations, therefore, establish the fact that patients with asthma react not with increased sensitivity but with an altered response (idiosyncrasy) to histamine.

THE EFFECTS OF SUBCUTANEOUSLY ADMINISTERED HISTAMINE ON THE CARDIAC RATE AND BLOOD PRESSURE IN MAN

Although the effect of subcutaneously administered histamine has been studied before, in order to compare the systemic as well as the cardiovascular effect of subcutaneously administered histamine with that of intravenously administered histamine, a few observations were made on the effect of the subcutaneous administration of histamine on the cardiac rate and arterial blood pressure. Ten young adults, after a control period of observation, were given 0.5 mg of histamine, and the effect on the cardiac rate, blood pressure and cutaneous vessels was observed. Both the systolic and the diastolic blood pressure showed a slight but transient fall, although this again was not observed in every instance. The cardiac rate per minute usually showed a maximal elevation of from 10 to 20 beats for from three to five minutes, after which

it returned to normal. The maximum intensity of the flush and the subjective reactions corresponded in general to the continuous intravenous injection with a rate of from about 0.03 to 0.05 mg. per minute. In three cases doses of both 0.5 and 1 mg. were administered at different times, and while a temporary slight fall in the systolic and diastolic pressure was observed after 0.5 mg., no change in the blood pressure was noted following 1 mg., although the elevation of the pulse rate was greater and of longer duration.

THE EFFECT OF ORALLY ADMINISTERED HISTAMINE ON MAN

Five normal volunteer subjects received gradually increasing amounts of histamine up to from 200 to 500 mg. No subjective or objective changes were observed. The pulse rate and the arterial blood pressure remained unaltered. Considering the massive doses administered, it may be concluded that histamine fails to produce any subjective effect or any changes in the cardiovascular system when administered in unusually large amounts orally.

COMMENT

The Sensitivity and Tolerance of Man to Histamine—The minimal single intravenous injection of histamine that exerts changes in the cerebral or facial blood vessels and the cardiac rate is 0.02 mg. of histamine phosphate, corresponding to 0.007 mg. of histamine base, while the maximal injection that can be tolerated and will produce a marked circulatory response with mild toxic manifestation is from 0.2 to 0.3 mg. On one occasion, the sudden injection of 1 mg. of histamine given by mistake, produced alarming symptoms for a few minutes. Changes due to the direct effect of histamine on the cardiovascular system last only from forty to eighty seconds as a rule, although some of the sequelae of these changes, such as headache, may persist longer.

A comparison of the sensitivity of the human and animal circulations to histamine is obviously difficult because of difference in the pharmacologic effect and experimental conditions. The fact that dogs, following the injection of 0.0054 mg. per minute per kilogram, show an intense toxic reaction (Koessler and Hanke²⁴) and that human subjects tolerate 0.004 mg. (histamine phosphate) per minute per kilogram, with an intense response but no alarming manifestations, suggests that the relative tolerance is essentially not different in dog and in man. Such small doses as 0.001 mg., given intravenously, produce a definite fall in the arterial blood pressure of the anesthetized cat (Feldberg⁹), while 0.1 mg. of histamine phosphate, corresponding to 0.03 mg. of the base,

²⁴ Koessler, K. K., and Hanke, M. T. The Intestinal Absorption and Detoxication of Histamine in the Mammalian Organism, *J. Biol. Chem.* **59** 889, 1924.

produces a definite but not a toxic response in man. From these responses to various dosages it is fair to assume that the susceptibility of man to histamine is not out of proportion to that of the higher mammals.

The rate of the entrance of histamine into the circulation is of fundamental importance in determining the intensity of the effect of histamine on the human cardiovascular system. The fact that an even rate of injection of histamine into the human circulation produces in general a uniform intensity of response, regardless of the duration of the injection, indicates that histamine is promptly converted into inert substances in the human body. The experiments presented also indicate that man tolerates, and hence is capable of destroying, as much or more than 20 mg of histamine in an hour, although one two-hundredths of this amount produces an intense reaction when injected suddenly. In this respect, the human body behaves similarly to that of the rabbit, as observed by Oehme²⁵. Although the evidence presented indicates that histamine becomes inert promptly after it enters the human circulation, the observations do not reveal the nature of its inactivation. The fate of histamine in the body is practically unknown. Intracutaneously injected histamine is not destroyed locally if the circulation is stopped by the application of a tourniquet. This suggests that all the tissue cells do not possess the ability to destroy histamine. Our experience suggests further that the blood is not the seat of the inactivation of histamine in man. Patients with cardiac decompensation, with a three to four-fold decrease in the velocity of the blood flow, are no less sensitive to histamine than persons with a normal circulation.

The fact that the minute blood vessels respond promptly but fleetingly to a single intravenous dose of histamine is weighty evidence that histamine is destroyed in the endothelial surface of the vascular wall. This conception is supported by two independent observations previously not fully understood by us¹³. Patients with emphysema show an increased peripheral vascular response to histamine, while in patients with hyperthyroidism the response is of less than normal intensity. In emphysema the capillary bed of the lungs is considerably decreased, while in hyperthyroidism, with the increased cardiac output, the surface of the pulmonary capillary bed is probably increased. All these observations point to the endothelial system of the vascular tree, and especially to the lungs, as important to the inactivation of histamine in man. Best²⁶ rather recently reported that the autolyzed lung tissue

25 Oehme, C. Ueber die Wirkungsweise des Histamins, *Arch f exper Path u Pharmacol* **72** 76, 1913.

26 Best, C. H. The Disappearance of Histamine from Autolyzing Lung Tissue, *J Physiol* **67** 256, 1929.

is capable of destroying considerable amounts of histamine. This action of the lung tissue, according to Best, possesses some of the characteristics of an enzyme. Liver and kidney *in vitro* also destroy histamine. Best did not determine the nature of the destruction of histamine by these tissues.

The fact that the oral administration of such large amounts of histamine as 500 mg fails to exert any appreciable influence on the cardiovascular system in man, and that such small amounts as 0.05 mg per minute in the blood stream exert a definite systemic effect, would suggest that histamine, taken internally, is inactivated before it reaches the general circulation. Two explanations are open. Either histamine is inactivated by a special function of the intestines before it enters the portal circulation, or it is destroyed by the liver before it enters from the portal to the greater circulation. Considering that in animals it has been shown repeatedly that the liver does not inactivate histamine to any extent (Popielski,²⁷ Koessler and Hanke²⁴ and Ivy and Javois²⁸) it seems probable that the human intestine, like that of animals, possesses a special capacity to destroy this substance. These observations in adults make questionable the validity of the theory that histamine is an important factor in "intestinal intoxication," as was suggested by the observations of Eppinger and Gutmann²⁹ Mellanby,³⁰ Rothler³¹ and Roske³². Such doubt can be disproved only by the demonstration of a decreased detoxicating or increased absorptive power of the intestines in patients with "intestinal intoxication."

In certain species of animals, under certain experimental conditions, histamine administered orally may enter the blood stream in sufficient concentration to induce changes in the circulatory mechanism (Meakins and Harington³³).

27 Popielski, L. B-Imidazolylathylamin und die Organextrakte. I. B-Imidazolylathylamin als mächtiger Erreger der Magendrüsen, *Arch f d ges Physiol* **178** 214, 1920, II. Einfluss der Säuren auf die Magensaftsekretion erregende Wirkung der Organextrakte, *ibid* **178** 237, 1920.

28 Ivy, A. C., and Javois, A. J. The Stimulation of Gastric Secretion by Amino Acids and Amines, *Am J Physiol* **68** 132, 1924, Contributions to the Physiology of Gastric Secretions. VI. The Stimulation of Gastric Secretion by Amines and Other Substances, *ibid* **71** 604, 1925.

29 Eppinger, H., and Gutmann, J. Zur Frage der vom Darm ausgehenden Intoxikationen, *Ztschr f Klin Med* **78** 399, 1913.

30 Mellanby, E. An Experimental Investigation on Diarrhoea and Vomiting of Children, *Quart J Med* **9** 165, 1916.

31 Rothler, H. Ueber das Verhalten der Amine bei Dyspepsie und Intoxikation, *Jahrb f Kinderh* **120** 162, 1928.

32 Roske, G. Ueber Bedingungen der Aminbildung durch *Bact coli*, *Jahrb f Kinderh* **120** 186, 1928.

33 Meakins, J., and Harington, C. R. The Relation of Histamine to Intestinal Intoxication. I. The Presence of Histamine in the Human Intestine. *J Pharmacol & Exper Therap* **18** 455, 1922.

Certain observations made in this study show that besides the chemical inactivation of histamine in man there is also a physiologic inactivation through the formation of a substance or substances antagonistic to histamine. It was frequently observed that if the infusion of histamine was continued for several hours, not only was there no accumulation of effect, but, on the contrary, the intensity of the response of the cardiovascular system gradually decreased. Often the mottled pale skin island within the flushed areas progressively increased, and the degree of elevation of the cardiac rate decreased. Furthermore, with cessation of the infusion there was a definite rise in the systolic, and especially in the diastolic, arterial blood pressure as compared with the normal control level, and the skin appeared remarkably pale. These observations suggest the production of an antagonistic substance in man as a response to the prolonged effect of histamine, a concept postulated on the basis of entirely different observations by Lewis³ and Burn and Dale². This hypothetical substance, although similar in its action to epinephrine, may be another vasoconstrictor substance. A second possibility, that this physiologic inactivation of histamine does not occur through chemical antagonism, but rather as an antagonistic response of the vasomotor nervous system, cannot be ruled out at present.

The Response of the Cardiovascular System—During the intravenous infusion of histamine at rates up to toxic doses such as from 10 to 20 mg per hour, the observed responses of the human circulation may be summarized as follows. The cardiac rate shows a progressive rise to a rate as high as from 130 to 140. Simultaneously, there is a moderate increase in the cardiac output. The circulating blood volume shows no appreciable change after the infusion of an average dose of 6 mg of histamine in one hour. The blood, however, as judged from the increased oxygen combining power, shows an increased concentration of hemoglobin, although the chemical constituents of the plasma remain unaltered. This indicates a transudation of small amounts of the blood plasma into the tissues. Because the circulating blood volume decreases slightly, the mean velocity of blood increases. The calculated mean circulation time was forty-two seconds before the administration of histamine and thirty-five seconds at the height of histamine effect, one hour after the onset of histamine injection, as was indicated in a previous report³⁴. Because the cardiac output is not proportional to the elevation of the heart rate, the stroke volume of the heart under the effect of histamine decreases slightly. The metabolic rate is accelerated, and the cardiac output increases about proportionately with the metabolism.

34 Weiss, S., Ellis, L. B., and Robb, G. P. Bodily Responses in Man During the Continuous Intravenous Administration of Histamine, *Am J Physiol* **90** 551, 1929.

Although the minute cerebral and cutaneous blood vessels show dilatation, the blood pressure as a rule is not lowered appreciably. In a number of instances a moderate lowering of the diastolic pressure was noted. The venous pressure was unaltered or slightly elevated.

The most significant of these findings is that man does not as a rule respond to histamine with a prompt fall in arterial blood pressure. One of the factors responsible for this maintenance of a sustained arterial pressure is that the peripheral dilatation of the minute vessels in man, in response to intravenous infusion of histamine, is not general. Whether other vascular areas besides the skin and the brain also respond with prompt dilatation is questionable. Amounts that produced dilatation of the minute vessels of the brain and of the skin failed to produce dilatation of the minute vessels of the abdominal organs in patients in whom laparotomy was performed under spinal anesthesia. Even in the skin vessels, the dilatation is more apt to occur in the venules than in the arterioles. But even if there is an increased blood flow through the skin the pressure in the minute vessels is not appreciably elevated, indicating only a relatively slight arteriolar dilatation as compared with the dilatation that follows the direct intracutaneous injection of histamine (Ellis and Weiss³⁵).

The second factor that prevents the lowering of the blood pressure is the prompt response of the heart with a moderately increased output. There is no decrease, but, on the contrary, an increase in the venous return of the blood to the right side of the heart in man in response to histamine. This behavior of the human heart is contrary to that of the cat's heart, which according to Dale and Laidlaw,⁷ shows a decreased systolic output due to a decreased venous return and not to primary cardiac weakness. Rühl³⁶ reported recently that the decreased cardiac output in dogs is mainly due to damage of the myocardium. However, the doses given by Rühl were unusually large. Changes in the complexes of the electrocardiogram indicate that in man histamine exerts a direct action on the coronary circulation or the myocardium even when administered in relatively small amounts. The more exact mechanism of this action of histamine on the human heart is not clear.

The demonstration of the unusual sensitivity of the human cerebral blood vessels is especially significant. Not only do the observations demonstrate that the minute vessels of the human brain are capable of responding promptly with alteration in their diameter, but quantita-

35 Ellis, L. B., and Weiss, S. The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation. In Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, *J. Clin. Investigation* 8: 47, 1929.

36 Rühl, A. Ueber Herzinsuffizienz durch Histamin, *Arch. f. exper. Path. u. Pharmacol.* 145: 255, 1929.

tive evaluation of these responses suggests that histamine and perhaps other substances through their local action may play a rôle in the regulation of the cerebral circulation in man

The great capacity of the human capillary venules up to the visible smaller veins to respond independently of the arterioles has also been clearly demonstrated. Such dilatation of the venules over a large area may shunt and shift considerable amounts of the blood volume. Thus one effect of the injection of histamine may be the shunting of a part of the circulating blood into one area, where the blood flow becomes relatively slow, in other areas, at the same time, it may be increased because of arteriolar dilatation. In our experience the dilation of the cutaneous venules with different dosages occurs more regularly than the dilatation of the arterioles

We wish to emphasize here, once more, that the effect of histamine on the minute vessels and on the circulation as a whole, when introduced into the blood stream, does not necessarily bear on the alleged rôle of histamine between cell function and local capillary activity

Histamine and Muscular Exercise—A number of the bodily responses of the cardiovascular system observed in man following the administration of histamine are similar to a certain extent to those that occur during and immediately following exercise. Increased cardiac rate, metabolism, velocity of blood flow and cardiac output are common physiologic characteristics of both exercise and histamine effect. The degree of the changes mentioned was less following the infusion of histamine than after exercise when related to the elevation of the cardiac rate. Furthermore, dyspnea may be intense in patients with circulatory failure following the administration of histamine, although in normal subjects this has not been observed even if the amount of histamine administered was sufficiently high to produce such a high cardiac rate as is observed only after intense muscular exertion associated with dyspnea. The lactic acid content of the blood failed to show any definite elevation during the histamine effect in contrast to muscular exercise. These facts, therefore, indicate that the analogy between the circulatory responses due to histamine and muscular exercise is only partial. The essential similarity is that histamine infusion, like muscular exercise, represents a burden on the human circulation

Respiration and Pulmonary Circulation—Study of various aspects of the respiration indicates that histamine produces no appreciable constriction of the bronchiolar tree in normal man. Since elevation in the intrapulmonary pressure, as well as increased pressure in the pulmonary artery, often reflects itself in changes in the venous pressure, the finding of unaltered or slightly elevated venous pressure together with the maintenance of a normal respiratory mechanism is evidence that hist-

amine up to toxic doses produces no marked constriction of the bronchioles or the minute vessels of the pulmonary circuit. On the other hand, in patients with bronchitis, bronchial asthma and certain forms of cardiac asthma, small amounts of histamine may induce bronchial and vascular constriction with an increase in the venous pressure. This suggests an altered response of the pulmonary system to histamine in these conditions, and the observations have an important bearing on the mechanism of anaphylaxis.

Histamine and Traumatic Shock—Dale and Laidlaw,⁷ in analyzing the effect of the continuous intravenous administration of histamine on anesthetized cats, observed that the circulatory responses in many respects are analogous to those observed in man in traumatic shock. An investigation of the nature of the histamine shock observed revealed that the observed cardiac failure and lowered blood pressure are results of an insufficient venous return, which is caused by stagnation of the blood in the capillaries and venules throughout the body, thus depleting the large arteries and veins. It is these circulatory characteristics that are most significant in shock. The increased hemoglobin content, which results from transudation of the whole plasma into the tissues, is considered by these authors not an essential, but a contributory, factor in the development of histamine shock. Hashimoto³⁷ confirmed the findings of Dale and Laidlaw that histamine increases the hemoglobin content of the blood without increasing the total solids of the plasma. Underhill and Kapsinow,³⁸ however, failed to observe an increased concentration of the blood if their dogs received a sufficient amount of water before the experiment. Similarly, in rabbits, Underhill and Roth³⁹ found no concentration of the blood induced by histamine. These apparently contradictory results are of great significance for, as pointed out, the capillary systems of different species reacts differently to histamine, and therefore it is easily probable that shock phenomena observed in cats may not be present in other animals.

Our observations on man revealed, in accordance with the findings of Dale and Laidlaw in the cat, a slight but definite increase in the hemoglobin content of the blood during the injection of histamine without any change in the protein, total solids or freezing point of the plasma. This indicates that under the influence of histamine the capil-

37 Hashimoto, H. Blood Chemistry in Acute Histamine Intoxication, *J Pharmacol & Exper Therap* **25** 381, 1925.

38 Underhill, F. P., and Kapsinow, R. The Influence of Water Deprivation upon Changes in Blood Concentration Induced by Experimental Shock, *Am J Physiol* **63** 142, 1922.

39 Underhill, F. P., and Roth, S. C. The Influence of Water Deprivation, Pilocarpin, and Histamine upon Changes in Blood Concentration in the Rabbit, *J Biol Chem* **54** 607, 1922.

laries of man permit the whole plasma to pass from the blood into tissues, spaces or lymphatics. In man, the amount of plasma that left the blood stream after the administration of from 6 to 10 mg of histamine in an hour must have been small, about 6 or 7 per cent of the normal plasma volume, as may be estimated from an increase in percentage of the hemoglobin combining power. The amount of plasma that left the blood stream was too small to have been demonstrable by the measurement of the blood volume by the dye method. The finding of an increased concentration of the blood due to transudation of plasma into the tissues does not indicate that the reaction of man to histamine is similar to that of anesthetized cats. This change, as also stated by Dale and Laidlaw, is not the characteristic feature of shock.

The important question as to whether or not man responds to histamine with a tendency to develop shock cannot be answered definitely from the observations presented. There are several significant findings, however, that strongly suggest that in normal subjects histamine does not induce a shocklike condition. If histamine is infused slowly and continuously into the circulation of the cat, the blood pressure falls promptly, even from small doses. This fall in pressure is early associated with a decreased cardiac output due to a decreased venous return and stagnation of a considerable amount of blood in the capillary system. These changes, which form the fundamental features of shock in cats, are not observed in man, even when such large amounts as from 10 to 20 mg of histamine are administered per hour for as long as two hours. In man, the arterial pressure does not fall, or the fall is but slight and venous pressures do not decrease, hence a depletion of the large arteries and veins does not occur. The cardiac output and the mean velocity of blood flow are not decreased but rather elevated, although small amounts of blood may occasionally stagnate in the cutaneous tissues. Even here, in many instances, the blood flow is increased. Evidence is lacking, therefore, that in man histamine acts as a generalized capillary depressant in doses that are capable of inducing marked systemic effects and of elevating the cardiac rate as high as 140 per minute. The elevated basal metabolism is also contrary to the reaction characteristic of experimental shock.⁴⁰

Objection may be made to this argument by supposing that higher doses than those applied in this study might induce the responses of shock. Such a possibility cannot be denied, however, considering the intensity of the general symptoms induced by the dosage applied and the absence of any observable tendency to shock it is questionable if this objection is valid.

40 Aub, J. C. Studies in Experimental Traumatic Shock. I. The Basal Metabolism, *Am J Physiol* **54** 388, 1920.

Even if higher toxic doses of histamine did induce characteristic shock in man, the argument that shock is due to a liberation and accumulation of histamine in the blood stream would not be supported. Such a response could not be considered as specific, as it is observed with numerous chemical agents when given in toxic doses.

Although Cannon⁸ offered evidence in support of the theory that traumatic shock is induced by a chemical substance, possibly histamine, it must be remembered that the changes in the minute blood vessels in shock are not characteristic of the effect of any single substance. A number of different chemical and physical agents might precipitate shock with identical circulatory changes, as Dale and Laidlaw⁷ rightly emphasized, "The existence of these points of community, in the action of substances so utterly unrelated chemically as histamine and certain metallic ions, forbids any assumption that the production of similar effects, by unknown constituents of some organ or tissue, indicates the presence therein of histamine itself, or of any substance chemically related to it. The similarity depends on the fact that all act on the endothelium and produce in it changes probably of the same general type." Recent evidence rather supports the concept that in traumatic shock the damage of the minute blood vessels is due to a progressive depression of the peripheral vasomotor mechanism. This may often occur without the presence of histamine or other chemical substances. The difference in degree of the relative susceptibility of the augmentor and inhibitory fibers to certain stimuli explains the depressor vascular responses of shock.⁴¹ These facts and our failure to reveal any specific tendency on the part of histamine to induce shock in man do not support the theory that histamine is essential to or responsible for traumatic shock in man.

SUMMARY AND CONCLUSIONS

1 A study of the systemic effects of histamine in man and a discussion of the physiologic and pathologic rôle of histamine, based on these observations, are presented.

2 Following the single or continuous intravenous administration of histamine, the latter is converted promptly into ineffective substances in the human body. The persistence of the action of histamine in man is of but a few minutes' duration. With uniform intravenous infusion, the bodily changes induced are practically stationary.

3 The minimal effective amount of histamine base in man is about 0.003 mg per minute, corresponding to a concentration of about

41 Smith, M. I. Studies on Experimental Shock with Especial Reference to Its Treatment, *J. Pharmacol. & Exper. Therap.* **32** 465, 1928; The Peripheral Vasomotor Mechanism in Experimental Shock, *ibid.* **34** 239, 1928.

1 2,000,000,000 parts in the circulating blood The maximal amount of histamine base, administered intravenously, that produces toxic manifestations is 0.15 mg per minute

4 The symptoms and signs of histamine intoxication in man are described

5 Relatively small amounts of histamine (0.003 mg per minute) cause a depression of the T waves of the complexes of the normal electrocardiogram With elevation of the dosage, the degree of depression increases, until the T wave may become inverted After a single intravenous dose, the change in the shape of the T wave is instantaneous with the arrival of histamine in the coronary circulation, and within one minute there is a tendency to return to the normal shape Changes in the T waves are not associated with any symptoms or signs referable to the heart

6 Histamine in amounts up to toxic doses in observations of two hours' duration fails, as a rule, to produce any lowering of the systolic arterial blood pressure The diastolic arterial blood pressure shows a tendency to fall, but in numerous instances it also remains unaltered With increasing amounts, there is a progressive rise in the cardiac rate

7 The venous pressure is either unaltered or slightly elevated

8 The effect of histamine on the cutaneous blood vessels is not uniform The most characteristic effect is a dilatation of the venules and small veins This effect is frequently independent of the dilator effect on the arterioles In one group of subjects, even toxic doses fail to produce a dilatation of the arterioles as judged by the cyanotic flush and lack of elevation of the surface temperature of the skin In a second group of subjects, the arteriolar dilatation develops when a larger dose, rather than one that produces a dilatation of the venules is administered In a third group, the dilatation of the arterioles and venules occurs simultaneously

9 As judged from the degree of elevation of the pressure in the minute vessels of the skin, the arteriolar dilatation following large intravenous doses of histamine is slight as compared with that following the local intracutaneous application of histamine base in a solution of 1:3,000

10 The different types of observations presented offer conclusive evidence that the minute cerebral vessels of man respond to histamine with conspicuous dilatation A certain parallelism exists between the sensitivity of the facial and the cerebral vessels to histamine In a number of instances the cerebral vessels were even more sensitive than the facial vessels, and cerebral arteriolar dilatation followed the intravenous administration of such small amounts as 0.003 mg of histamine base

11 The cardiac output per minute following the intravenous infusion of from 0.02 to 0.03 mg of histamine base per minute increases by an average of 15 liters, or to 20 per cent above the normal value. Simultaneously, there is a slight fall in the stroke volume. The mean velocity of blood flow shows a slight but distinct increase.

12 The basal metabolism becomes elevated and may reach values 50 per cent above the normal. There is a slight fall in the respiratory quotient.

13 A study of the chemical constituents and certain physical characteristics of the blood, together with its hemoglobin combining power, indicates that with the administration of histamine, transudation of small amounts of whole plasma occurs. This amount is too small to be demonstrated by the measurements of the total blood volume with the dye method.

14 Histamine produces no demonstrable changes in the pulmonary ventilation or in the state of the bronchioles of normal persons, but has a definite bronchial constrictor effect on patients with bronchitis, bronchial asthma, emphysema and cardiac asthma.

15 Histamine, when administered orally in massive doses, is ineffective, hence, its rôle in intestinal intoxication is highly questionable.

16 Evidence is presented that during the administration of histamine substances are formed or vasomotor reflexes develop which act antagonistically to histamine.

17 The degree of peripheral vascular dilatation in man induced by histamine is not marked, and the distribution is not widespread. The vasodilator effect of histamine is promptly counteracted by an increase in the cardiac output and in other regulatory functions.

18 A certain parallelism exists between the circulatory responses that follow exercise and those that follow the injection of histamine, but this parallelism is incomplete.

19 The vascular and other bodily responses induced by histamine in man differ fundamentally from those observed in anesthetized cats and in patients with traumatic shock. The rôle of histamine in traumatic shock is therefore considered doubtful.

AVITAMINOSIS

IV THE EFFECT OF A DEFICIENCY OF THE VITAMIN B COMPLEX ON THE LIPID METABOLISM AND GLYCOGEN CONTENT OF THE LIVER OF THE ALBINO RAT ^{*}

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In previous communications we have demonstrated that the main biochemical changes in the albino rat suffering from a deficiency of the vitamin B complex are anhydremia associated with a disturbance in hematopoietic function ¹ and, in uncomplicated vitamin B deficiency, a marked reduction in the glycogen content of the liver ². Since in such avitaminosis the most pronounced symptom complex is anorexia, the tentative conclusion made was that the pathologic changes encountered may have been, at least in part, produced indirectly through a reduction in food consumption. In this and in the communication following, experimental evidence is submitted on studies carried out by a method which eliminated the plane of nutrition as a complicating factor. Weaned albino rats, weighing from 50 to 60 Gm and about 4 weeks of age, were transferred from our stock diet 1 ³ to diet 1751, satisfactory in every respect, with the exception of vitamin B complex, and of the following composition: casein, ⁴ 20, salts, 185, ⁵ casein, 4, butterfat, 10, and dextrin, 66. Littermates of the same sex were restricted to the same daily water and food intake of that diet, but received in addition an abundance of the vitamin B complex by the replacing of 10 per cent of the dextrin in ration 1751 with dried baker's yeast. Since the plane of nutrition was controlled, the difference in physiologic and pathologic results obtained in these two groups of animals must be attributable to

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^{*} From the Departments of Agricultural Chemistry and Home Economics University of Arkansas

1 Sure, B., and Smith, M. E. J Biol Chem **82** 307, 1929. Sure, B., Kik, M. C., and Walker, D. J. *ibid* **82** 287, 1929

2 Sure, B., and Smith, M. E. Proc Soc Exper Biol & Med **27** 861, 1930

3 Sure, B. J Biol Chem **69** 65, 1926

4 Purified by extraction for ten days with acidulated water

5 McCollum, E. V. and Simmonds, N. J Biol Chem **33** 63, 1918

the specific influence of the vitamin B complex. Employing such technic, it became apparent that in this avitaminosis there is produced a lipemia, characterized by a rise in the fatty acids, cholesterol and lecithins of the blood, also that there is a considerable reduction in the glycogen content of the liver.

The blood was obtained by peripheral bleeding according to the technic previously described.⁶ For the various determinations of lipids, even employing micromethods, 1 cc of blood was found necessary. Such an amount of blood represented a large proportion of the total volume of the small avitaminotic animals that were losing weight. Therefore, in

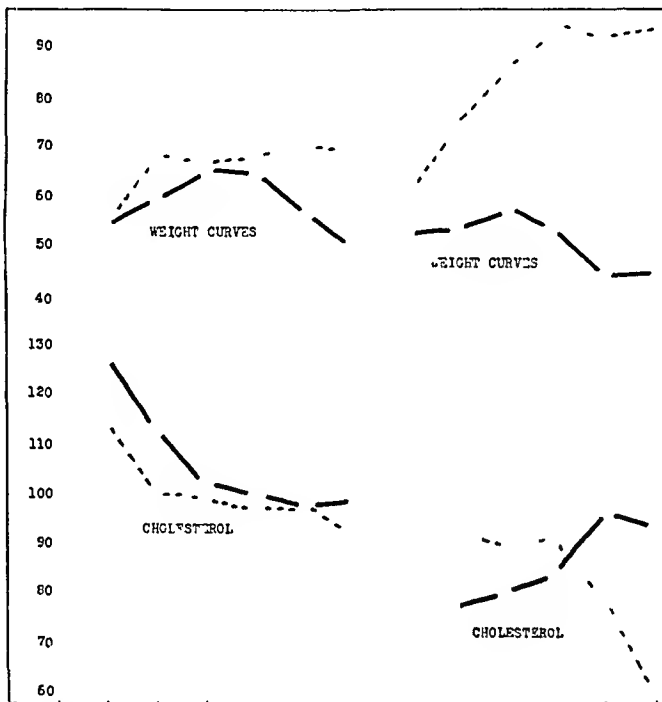


Chart 1—Weight and cholesterol curves for groups 1938-1939 (left) and 1966-1967 (right). In this and the following charts the heavy line indicates the pathologic group and the dotted line the control group. Each division on the horizontal scale indicates one week. Body weights are expressed in grams.

order to avoid any accompanying anemia that might be precipitated by such a procedure, the blood was pooled from two littermates of the pathologic group, and at the same time samples were taken from two littermate controls. Of 1 cc one-half was used for the cholesterol determination and the other half for the analyses of lecithin, fatty acids and the iodine number, the latter giving an index of the unsaturated fatty acids. The cholesterol was determined by the Lieberman and

6. Sure B, Kik, M. C., and Walker, D. I. *J. Nutrition* 1:299, 1929.

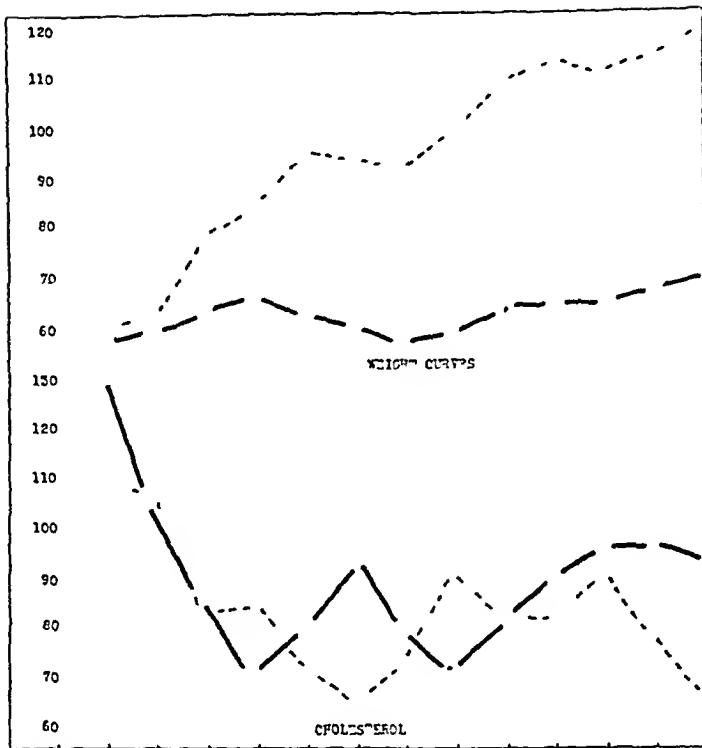


Chart 2—Weight and cholesterol curves for group 1940-1941 Each division on the horizontal scale indicates one week

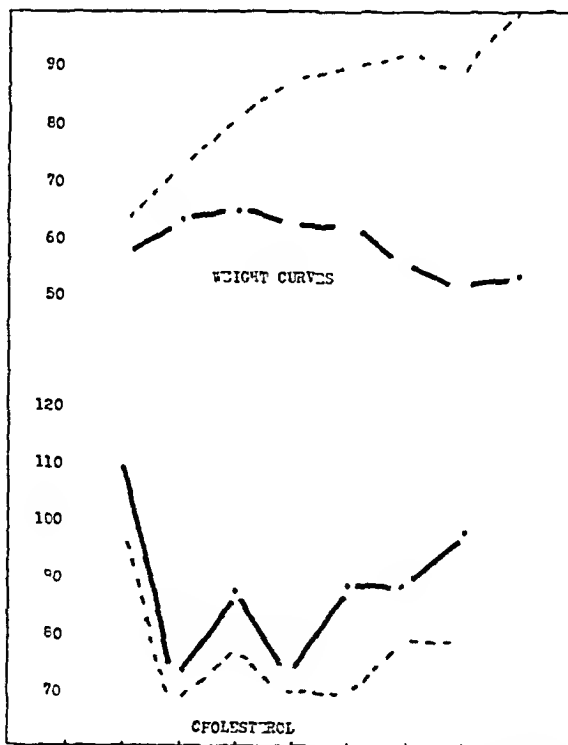


Chart 3—Weight and cholesterol curves for group 1966-1967 Each division on the horizontal scale indicates one week

Burchard method,⁷ the lecithin by the Fiske and Subbarow method⁸ and the fatty acids by the methods of Bloor, Pelkan and Allen⁹ and Stoddard and Drury¹⁰ One modification was found helpful in the determination of fatty acids They were titrated in a benzene solution with two-hundredth-normal potassium hydroxide made with absolute alcohol

At the termination of the experiment the animals were killed and the glycogen of the livers was analyzed by a modified method of Pflueger used by Cori and Cori¹¹

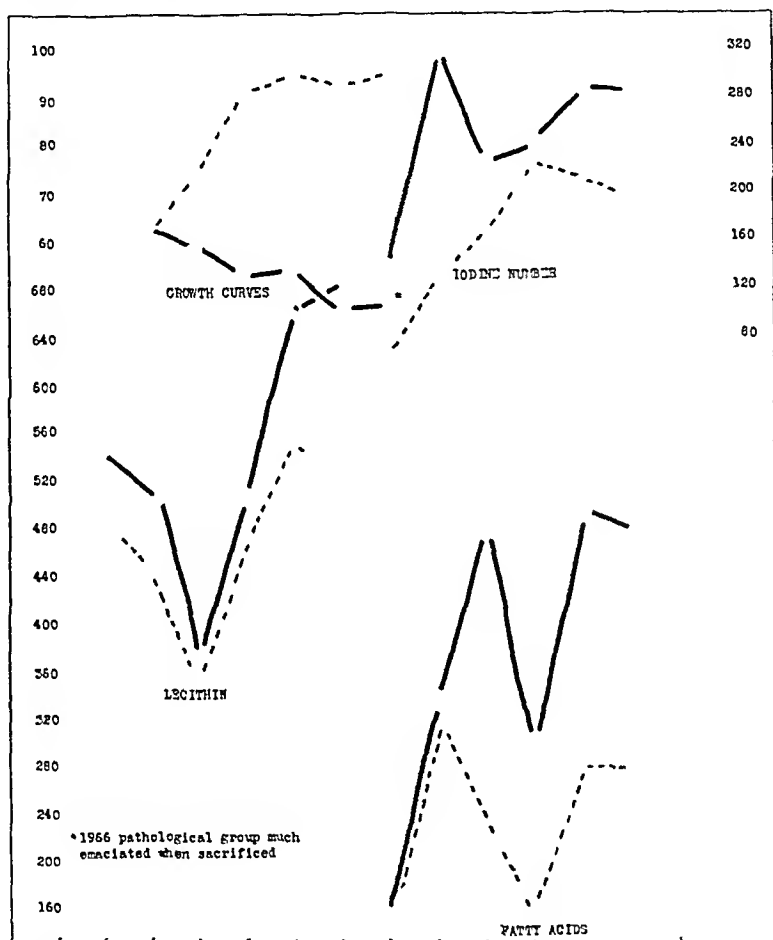


Chart 4—Curves of growth, iodine number, lecithin and fatty acids for group 1966-1967 Each division on the horizontal scale indicates one week

The results are presented in charts 1 to 6, inclusive, and in tables 1 and 2

7 Hawk and Bergeim *Physiological Chemistry*, ed 9, Philadelphia, P Blakiston's Son & Company, p 281

8 Fiske, C H, and Subbarow, Y *J Biol Chem* **66** 375, 1925

9 Bloor, W R, Pelkan K F, and Allen, D M *J Biol Chem* **52** 191 1922

10 Stoddard, J L, and Drury, P A *J Biol Chem* **84** 741 1929

11 Cori, D F, and Cori, G T *J Biol Chem* **70** 557, 1926

The weight curves shown in all the charts represent the average growth of two littermates of the same sex. Similarly, the curves showing the concentration of the various lipid constituents of the blood indicate the average figures for two littermate rats of the same sex. This is true of the curves for the control animals (shown in dotted lines) and the pathologic animals (drawn in heavy lines).

It is quite clear from all the charts that, since the plane of nutrition was controlled, the vitamin B complex *per se*, furnished by dehydrated baker's yeast, produces a considerable effect on growth. Some groups in as short an interval as from five to six weeks more than doubled their weight by virtue of the presence of the water-soluble vitamins supplied by the yeast, as compared with the failure of growth of littermate groups on the same diet and the same daily food and water intake that were denied the vitamin B complex.

TABLE 1—*Summary of Results on the Influence of a Deficiency of the Vitamin B Complex on the Lipid Metabolism of the Albino Rat, Expressed as Milligrams per Hundred Cubic Centimeters of Blood*

	Avitaminotic Animals		Controls on Same Plane of Nutrition, but Which in Addition Received Vitamin B Complex	
	Range	Average	Range	Average
Cholesterol	81*-118†	93‡	72*-109†	75‡
Lecithin	361-610	473	319-515	406
Fatty acids	273-615	420	193-472	338
Iodine number (of fatty acids)	170-469	310	117-275	177

* Represents the average of all the minimum figures

† Represents the average of all the maximum figures

‡ Represents the average of all the determinations

LIPID METABOLISM

Cholesterol—While there was considerable fluctuation in this constituent during the experimental period in both the control and pathologic rats, the concentration of cholesterol was much higher in the avitaminotic animals, being least, by comparison with the controls, in group 1938-1939 and most in group 1966-1967 (chart 1). In group 1940-1941 the cholesteremia occurred during the last five weeks of the avitaminosis.

Lecithin and Fatty Acids—It is quite apparent from charts 4, 5 and 6 that there is a higher concentration of both of these lipid constituents throughout the experimental period in the vitamin B-deficient animals,¹² It is also evident that, in the case of the fatty acids, the lipemia begins as early as from the first to the second week of vitamin B-depletion.¹²

Iodine Number—The iodine number of the fatty acids represents the degree of unsaturation, and from the data submitted, we can con-

¹² The term vitamin B is used here in the sense of the group of water-soluble vitamins referred to in this paper as the vitamin B complex.

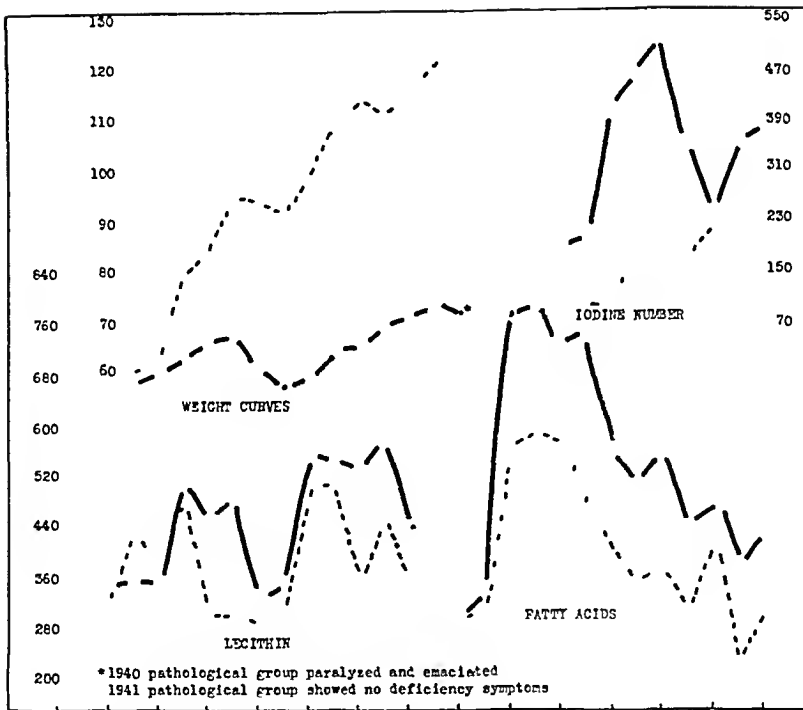


Chart 5—Curves of weight, iodine number, lecithin and fatty acids for group 1940-1941 Each division on the horizontal scale indicates two weeks

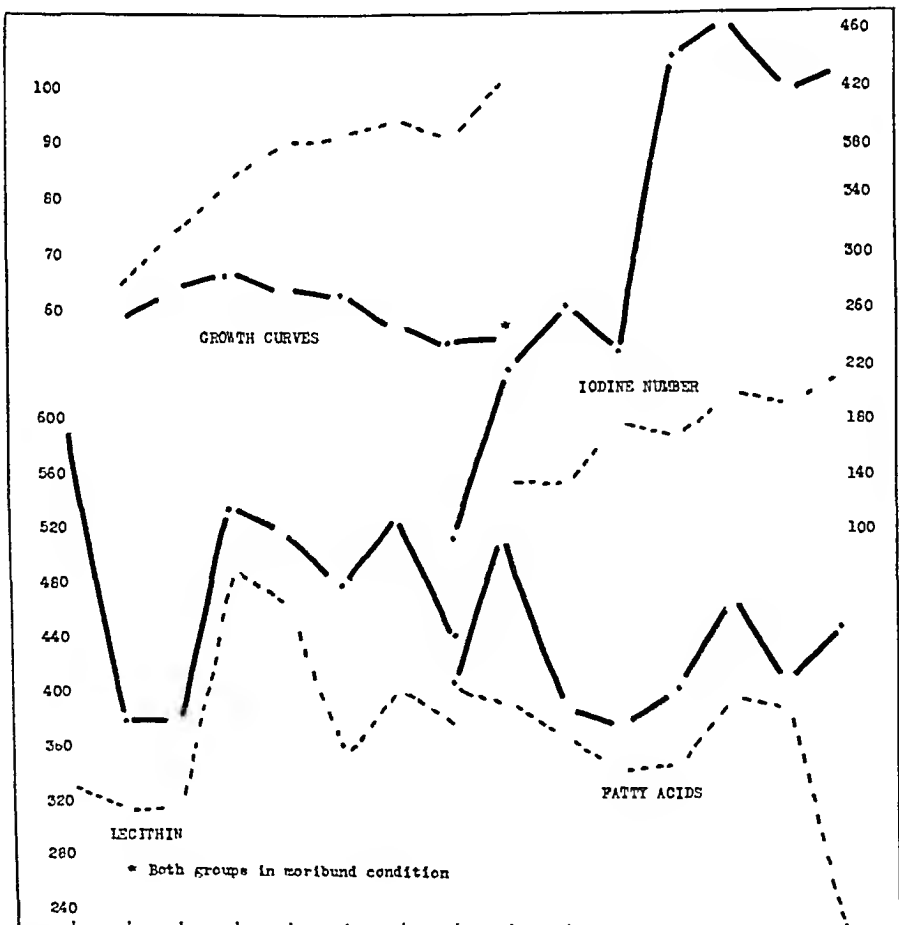


Chart 6—Curves of growth, iodine number, lecithin and fatty acids for group 1964-1965 Each division on the horizontal scale indicates one week

clude that a considerable proportion of the lipemia due to fatty acids belongs to the unsaturated series, since the iodine number of the blood of the avitaminotic animals was always higher than that of the controls

In table 2 is presented a summary of the average figures for all the determinations throughout the period of experimentation, also the average minimum and maximum figures which constitute the range. An analysis of this table discloses the fact that in the disturbance of fat metabolism during vitamin B¹² deficiency the fatty acids show the greatest rise, the cholesterol the next greatest and the lecithins the least

TABLE 2—*Specific Effect of Deficiency of Vitamin B Complex on the Glycogen Content of the Liver*

Group	Animal	Age, Days	Sex	Weight, Gm	Weight of Liver, Gm	Weight of Dextrose per Liver, Mg	Dextrose per 100 Gm of Liver, Mg	Dextrose, per Cent of Body Weight, Mg
Pathologic Control	7515	65	♀	51	1 5876	7 91	498 24	15 51
	7516	66	♀	72	1 9735	13 78	698 25	19 14
Pathologic Control	7517	64	♂	51	1 7146	10 07	587 31	19 75
	7518	65	♂	68	2 1812	14 28	654 68	21 00
Pathologic Control	7519	116	♂	50	1 9664	8 01	407 34	16 02
	7520	117	♂	100	2 7828	11 33	407 14	11 33
Pathologic Control	7521	122	♀	94	2 5000	8 26	330 40	8 79
	7522	123	♀	147	4 1298	12 39	300 01	8 43
Pathologic Control	7631*	84	♂	54	2 0271	3 24	159 83	6 00
	7632	85	♂	102	3 4464	11 62	337 16	11 39
Pathologic Control	7633*	71	♀	43	1 6110	1 31	112 35	4 21
	7634	72	♀	79	2 7533	4 12	149 64	5 22
Pathologic Control	7635*	64	♀	36	1 5309	2 75	179 63	7 64
	7636	65	♀	97	3 3289	14 13	424 46	14 56
Pathologic Control	7637*	67	♂	55	2 7332	4 40	160 98	8 00
	7638	68	♂	92	3 3093	15 52	463 98	16 87

* Killed in moribund condition

GLYCOGEN CONTENT OF THE LIVER

Our observations on the influence of vitamin B¹² deficiency on the glycogen content of the liver are summarized in table 2. The results are expressed in milligrams of dextrose per liver, per hundred grams of liver and per hundred grams of body weight. All the avitaminotic animals showed a considerable reduction in the glycogen, expressed as the amount of dextrose per liver. That the reduction in liver glycogen was not just proportional to the reduction of the weight of the liver is evident in that in 75 per cent of the cases the reduction of liver glycogen was much greater than the loss of liver weight. This is indicated by the figures showing the amount of dextrose per hundred grams of liver. The reduction of liver glycogen in the pathologic rats was also greater than the loss of body weight in 75 per cent of the cases. Since the plane of nutrition of the control animals that received the vitamin B complex

in the diet was restricted to that of the pathologic animals, the pronounced reduction in the glycogen content of the liver is attributable to the specific influence of this avitaminosis

Since vitamin B deficiency is seldom found to exist in this country in an accentuated form as it occurs in the orient, manifested as a specific disease, beriberi, it is quite possible that for lack of cleancut clinical symptomatology, many borderline cases are missed. It is therefore suggested to the clinician that a chemical study of the blood lipids may be an aid to the prognosis of the need of vitamin B therapy, particularly in cases of malnutrition, associated not necessarily with a chronic anorexia, but with a lack of normal appetite. It is recognized, however, that cholesteremia is found in such diseases as diabetes and in chronic parenchymatous nephritis,¹³ also that it may be present in other deficiency diseases. Therefore, it will be necessary to have the assurance that there is an adequate intake of vitamins A and D, which can be readily furnished by cod liver oil, and vitamin C, which can be supplied by orange and tomato juice, and that the patients are free from other diseases before a lipemia, if found, can be ascribed to vitamin B deficiency.

We are at present studying the lipid metabolism in other deficiency diseases.

SUMMARY

1 A deficiency of the vitamin B complex per se produces in the albino rat a lipemia, characterized by an increase in fatty acids, the iodine number of fatty acids, cholesterol and lecithins. The increase in concentration is in the order named.

2 A deficiency of the vitamin B complex per se produces in the albino rat a marked reduction in the glycogen content of liver.

3 It is suggested that the lipemia in the avitaminosis studied may have a clinical application.

13 Campbell, J. M. H. *Quart J Med* **18** 393, 1925.

AVITAMINOSIS

V THE SPECIFIC EFFECT OF VITAMIN B DEFICIENCY ON THE DIFFERENTIAL COUNT OF THE ALBINO RAT[†]

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AND

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In a recent communication Sure, Thatcher and Walker¹ have reported that in uncomplicated vitamin B deficiency there are produced a lymphopenia and a corresponding polymorphonuclear leukocytosis. The conclusion was, however, tentatively reached that such changes may be an expression of inanition. In this article we are submitting evidence showing that such a phenomenon is a manifestation of a deficiency of vitamin B per se.

Three groups of littermate rats of the same sex were studied in sets of four. The first animal received a diet satisfactory in every respect with the exception of vitamin B, 10 per cent autoclaved dehydrated yeast in the ration having supplied an adequacy of vitamin G. The second animal received the same diet and was restricted to the same amount of food and water daily as the first, but instead received the same proportion of untreated yeast in the ration, thus being supplied an abundance of vitamins B and G. The only limiting factor in the diet of the first animal was then vitamin B, and the difference in growth and the leukocyte picture of the blood between the first and second animals was then due to the specific influence of vitamin B, since the plane of nutrition was controlled. The third animal received the same diet and the same amount of food daily as the second animal, but was allowed water ad libitum. Consequently, any difference in physiologic and biologic findings between the second and third animal is attributable to the luxury consumption of water. The fourth animal was allowed the same diet as the second animal, but was unrestricted in its daily food and water intake. Therefore, the biochemical changes produced in the

* Submitted for publication, June 27, 1931

* Research paper no 237, Journal Series, University of Arkansas

[†] From the Department of Agricultural Chemistry, University of Arkansas

1 Sure B, Thatcher, H S, and Walker, D J. Avitaminosis. I. Pathologic Changes in Nursing and in Weaned Albino Rats Suffering from Vitamin B Deficiency, Arch Path **11** 413 (March) 1931

second animal as compared with the fourth are due to undernutrition or inanition

In tables 1 to 4 we are giving typical results of one of these four group experiments

TABLE 1—*The Differential Leukocyte Count of Rat 7483 (Female) on a Diet Satisfactory in Every Respect with the Exception of Vitamin B*

Date	Age	Weight	Poly-morpho-nuclears	Lympho-cytes	Large Mono-nuclears	Eosino-phils	Baso-phils
11/19/30	58	92	20	75	2	3	0
11/26/30	65	90	17	80	1	2	0
12/ 3/30	72	86	20	74	4	2	0
12/10/30	79	86	27	69	3	0	1
12/17/30	86	89	24	74	0	2	0
12/24/30	93	93	22	76	2	0	0
12/31/30	100	91	20	80	0	0	0
1/ 7/31	107	96	26	74	0	0	0
1/14/31	114	91	31	66	0	2	1
1/21/31	121	97	34	64	2	0	0
1/28/31	128	100	35	60	2	2	1
2/ 4/31	135	108	38	59	3	0	0
2/11/31	142	109	40	54	2	3	0
2/25/31	156	105	36	58	2	3	1
3/12/31	171	99	39	56	3	2	0
3/26/31	185	77	40	54	3	2	1
4/ 8/31	198	78	42	58	0	0	0
4/15/31	205	73	40	56	3	1	0

TABLE 2—*The Differential Leukocyte Count of Rat 7484 (Female) on the Same Diet and the Same Food and Water Intake as Its Littermate, Rat 7483, but Which in Addition Received an Abundance of Vitamin B in Its Ration*

Date	Age	Weight	Poly-morpho-nuclears	Lympho-cytes	Large Mono-nuclears	Eosino-phils	Baso-phils
11/19/30	58	89	18	80	1	0	1
11/26/30	65	87	27	73	0	0	0
12/ 3/30	72	88	28	65	2	4	1
12/10/30	79	85	33	62	3	2	0
12/17/30	86	93	30	66	2	2	0
12/24/30	93	98	23	64	0	2	1
12/31/30	100	94	21	78	1	0	0
1/ 7/31	107	108	18	80	0	2	0
1/14/31	114	110	20	77	2	0	1
1/21/31	121	110	21	75	2	1	1
1/28/31	128	115	24	71	2	2	1
2/ 4/31	135	115	20	75	2	3	0
2/11/31	142	124	21	75	2	2	0
2/25/31	156	135	23	75	2	0	0
3/12/31	171	127	24	73	2	1	0
3/26/31	185	125	22	76	0	2	0
4/ 8/31	198	115	20	77	0	2	1
4/15/31	205	114	17	80	2	0	1

The animals were bled peripherally, and the differential counts were made, the Wright stain being used. No differentiation was made between the small and large lymphocytes, all such cells having been grouped under lymphocytes.

In a previous publication, Sure Kik and Walker demonstrated that there is no appreciable change in the total leukocyte count in this avitaminosis; therefore, the total count was deleted in this investigation.

It is apparent from the representative data submitted here that vitamin B per se produces an effect on growth, also that in this avitaminosis there results a lymphopenia to the extent of about 20 per cent with a corresponding polymorphonuclear leukocytosis, which is a direct

TABLE 3—*The Differential Leukocyte Count of Rat 7485 (Female) on the Same Dietary Regimen as Its Littermate, Rat 7484, the Daily Food of This Animal Was Restricted to That Given Females 7483 and 7484, but Water Was Allowed ad Libitum*

Date	Age	Weight	Poly morpho nuclears	Lympho- cytes	Large Mono nuclears	Eosino phils	Baso phils
11/19/30	58	90	17	80	0	3	0
11/26/30	65	94	18	79	0	3	0
12/ 3/30	72	95	20	78	0	2	0
12/10/30	79	86	26	73	0	0	1
12/17/30	86	91	24	71	2	3	0
12/24/30	93	94	26	68	2	2	2
12/31/30	100	91	18	81	1	0	0
1/ 7/31	107	101	20	78	0	2	0
1/14/31	114	101	20	79	0	1	0
1/21/31	121	99	22	78	0	0	0
1/28/31	128	105	23	73	2	2	0
2/ 4/31	135	112	26	69	2	2	1
2/11/31	142	120	28	70	2	0	0
2/25/31	156	121	20	78	2	0	0
3/12/31	171	125	24	72	2	1	1
3/26/31	185	127	23	75	2	0	0
4/ 8/31	198	117	18	80	0	2	0
4/15/31	205	117	19	81	0	0	0

TABLE 4—*The Differential Leukocyte Count of Rat 7486 (Female) on the Same Diet as Was Furnished Females 7484 and 7485, This Rat Was Unrestricted as to Its Daily Food and Water Intake, This Is the Positive Control*

Date	Age	Weight	Poly morpho nuclears	Lympho- cytes	Large Mono nuclears	Eosino phils	Baso phils
11/19/30	58	103	18	79	2	0	1
11/26/30	65	114	25	71	1	3	0
12/ 3/30	72	127	29	66	3	2	0
12/10/30	79	131	30	66	3	0	1
12/17/30	86	139	21	76	1	2	0
12/24/30	93	147	18	77	3	2	0
12/31/30	100	152	24	74	0	2	0
1/ 7/31	107	155	20	78	1	0	1
1/14/31	114	157	21	77	0	2	0
1/21/31	121	167	23	73	2	2	0
1/28/31	128	167	24	70	4	2	0
2/ 4/31	135	168	30	62	5	2	1
2/11/31	142	172	21	74	2	3	0
2/25/31	156	174	24	72	1	2	1
3/12/31	171	170	23	75	0	1	1
3/26/31	185	174	20	76	4	0	0
4/ 8/31	198	173	21	79	0	0	0
4/15/31	205	177	20	75	2	3	0

expression of vitamin B deficiency and not of inanition. The changes in the large mononuclears or monocytes and in the eosinophils and basophils are insignificant in this dietary deficiency. It is also evident that a liberal supply of water does not change the blood picture. The surprising fact in this study is that no apparent change was observed

in the differential count as a result of undernutrition. If a change were produced, rat 7486, whose intake was not restricted, should have shown different results from rat 7484, which was restricted to the same complete synthetic diet, but the lymphocyte-polymorphonuclear ratio was not disturbed throughout the whole experimental period.

In addition to the three groups of four, we have studied four sets of pairs according to the technic described in the first part of the paper. However, we were unable to substantiate these findings in four pairs of animals that were depleted of the vitamin B complex, i. e., on a diet deficient in both vitamins B and G, the reason probably being that the animals on such a dietary regimen succumbed before an opportunity was afforded for pathologic changes to be demonstrable in the blood stream.

SUMMARY

A deficiency of vitamin B per se produced in the weaned albino rat a lymphopenia to the extent of about 20 per cent, with a corresponding polymorphonuclear leukocytosis. No demonstrable changes were found in this avitaminosis in the monocytes, eosinophils or basophils.

EFFECT OF LIGATION OF THE PAROTID DUCTS ON THE CARBOHYDRATE TOLERANCE OF NORMAL DOGS*

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CHICAGO

During the period, about forty years ago, when Minkowski¹ was establishing a probable relationship between the pancreas and diabetes, two Italian workers, de Renzi and Reale,² reported diabetes in dogs following the extirpation of the salivary glands and of the duodenum. Minkowski felt that the removal of the duodenum could not be effected without at the same time materially damaging the pancreas. He repeated the experiments on the salivary glands and found a mild (from 1 to 3 per cent), inconstant, transient glycosuria after removal of these glands. He concluded that this glycosuria was nonspecific, that it was incidental to the operation or the anesthetic, and that the salivary glands had nothing to do with the control of the sugar metabolism. This is the view that, with very few exceptions, has prevailed regarding the function of the salivary glands.

In 1907, Ferrannini³ reported a case of "salivary diabetes" in which the patient suffered from an excessive flow of saliva (several liters in twenty-four hours) that contained dextrose. Later it was found that glycosuria alternated with and replaced the glycosialorrhea. His interest being aroused in a possible reciprocal relationship between the salivary glands and the pancreas, Ferrannini entrusted to his assistant, Farioni,⁴ a series of investigations concerning the function of the

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† Associate in Surgery, Northwestern University Medical School

1 Minkowski. Weitere Mitteilungen ueber den Diabetes mellitus nach Extirpation des Pankreas, Berl klin Wchnschr **29** 90, 1892

2 de Renzi and Reale. Ueber den Diabetes mellitus nach Extirpation des Pankreas, Berl klin Wchnschr **29** 560, 1892

3 Ferrannini, A. Glycosialorrhée de sécrétion interne des glandes salivaires, Rev méd de Paris **31** 269, 1911, Glycosialia and Glycosialorrhea, Riforma med **44** 1249, 1928

4 Farioni. Funzione endocrina delle glandole salivari ed eliminazione degli zuccheri, Rev crit di clin med **12** 577 and 593, 1911

salivary glands These studies showed that extracts of salivary glands of cattle exerted a glyco-inhibitory action in rabbits, preventing or controlling glycosuria following the administration of epinephrine, phlorhizine and morphine In vitro the extract exhibited marked glycolytic action (from 65 to 70 per cent) on different sugars On the basis of these findings, Ferriannini postulated an endocrine action of the salivary glands analogous to that of the pancreas

No significant confirmation of these findings appeared until 1924, when Goljanitzki⁵ published results of experiments on the "substitution of endocrine glands" Among other things, he found that removal of both parotid and submaxillary glands in rabbits led to rapid emaciation and death, and glycosuria was noted Ligation of the parotid duct prevented glycosuria due to epinephrine In one patient with diabetic gangrene, ligation of the parotid duct was done, with strikingly beneficial results In a later publication additional cases were described in which ligation of the parotid ducts and transplantation of the submaxillary gland seemed to influence favorably the symptoms of diabetes

Mansfeld,⁶ of Budapest, in 1928, sought a surgical cure for diabetes He found that ligation of part of the pancreas increased the production of insulin He reasoned that obstruction to the external secretion resulted in increased internal secretion On the basis of this and of the fact that glands of internal secretion ontogenetically and phylogenetically are external secretory glands which develop an endocrine function when they lose their excretory ducts, he assumed that any gland of external secretion could be converted into one of internal secretion by depriving it of its excretory duct Because the salivary glands resemble the pancreas embryologically and morphologically, and because both are concerned with digestion of carbohydrates, he anticipated that ligation of their ducts would convert them into endocrine glands with an insulin-like secretion He accordingly ligated the parotid ducts of two dogs, and found that the blood sugar levels, particularly the starvation levels, were lowered Later, the ligated glands were extirpated, and the sugar levels returned to their preoperative values Two additional dogs were depancreatized, and the parotid ducts were then ligated, with resulting control of the diabetes Total extirpation

5 Goljanitzki, J. A. Zur Frage des Ersatzes der endokrinen Druesen, *Arch f klin Chir* **130** 763, 1924, Zur Frage der inneren Sekretion der Speicheldruesen und ihre klinische Bedeutung, *Deutsche Ztschr f Chir* **191** 79, 1925 Goljanitzki and Smirnowa Weitere Erfahrungen mit der chirurgischen Behandlung des Diabetes, *Ztschr f klin Med* **105** 661, 1927

6 Mansfeld, G., and Szirtes, L. Ueber die Beziehungen zwischen aeusserer und innerer Sekretion der Druesen, *Arch f exper Path u Pharmakol* **130** 1 and 28, 1928 Mansfeld, G. Versuche zu einer operativen Behandlung des Diabetes, *Klin Wchnschr* **7** 14, 1928 Mansfeld, G., and Schmidt, E. Versuche zu einer operativen Behandlung des Diabetes, *Klin Wchnschr* **7** 1457, 1928

of the pancreas in an animal in which the parotid ducts were ligated, however, produced just as severe diabetes as in normal animals. It was thought, therefore, that the action was an indirect one—a substance being produced in the parotid glands that stimulated the pancreas to increased function. Two patients were operated on, but the results were not stated. Seelig,⁷ of Berlin, repeated these experiments and confirmed Mansfeld's findings. He subsequently reported a series of eighteen cases of diabetes in which ligation of the parotid ducts was done, with definite amelioration of symptoms in some of the cases. The number of cases was too small and the period of observation too short to permit the drawing of definite conclusions. De Takats⁸ confirmed Mansfeld's findings following ligation of the tail of the pancreas, and recently reported two cases of juvenile diabetes in which the clinical course of the disease was favorably influenced by this operation.

The results reported following ligation of the parotid ducts seemed to my co-workers and me to be of sufficient significance to warrant further investigation. Accordingly, determinations of sugar tolerance were made in a series of dogs before and after ligation of both parotid ducts. Healthy, normal animals were selected for this work, of sufficient size to permit repeated venipunctures for the injection of sugar solutions and for the collection of blood samples. The animals were kept on a known controlled diet, consisting of lean meat and milk. They were fed once daily, at the same hour. In the earlier experiments, the sugar for the dextrose tolerance tests was administered by mouth. Later, to obviate irregularities in the rate of absorption, all dextrose solutions were injected intravenously at a timed rate. Blood samples were taken immediately before the injection of dextrose, and at intervals of fifteen, thirty, forty-five, sixty and one hundred and twenty minutes thereafter. The determinations of the blood sugar were done by the modified Folin-Wu method, in the chemical laboratory of the Nelson Morris Institute for Medical Research.

It was found that repeated determinations of dextrose tolerance, by the method described, gave results that usually checked very closely. We are aware that this is in variance with the experience of others. We feel that if conditions are maintained as nearly uniform as possible, most dogs will give blood sugar curves that coincide very closely.

7 Seelig, S. Ueber Beziehungen zwischen Parotis, Pankreas, Blutzucker und Diabetes mellitus, *Klin Wchnschr* **7** 1228, 1928, Zur chirurgischen Behandlung der Zuckerkrankheit, *Arch t klin Chir* **157** 322, 1929.

8 de Takats, G. Ligation of Tail of Pancreas in Juvenile Diabetes. *Endocrinology* **14** 255 (July-Aug.) 1930. de Takats, G., Hannett, F., Henderson, D., and Seitz, I. J. Correlations of Internal and External Pancreatic Secretion. IV. Effect of Isolation of Tail of Pancreas on Carbohydrate Metabolism, *Arch Surg* **20** 866 (May) 1930.

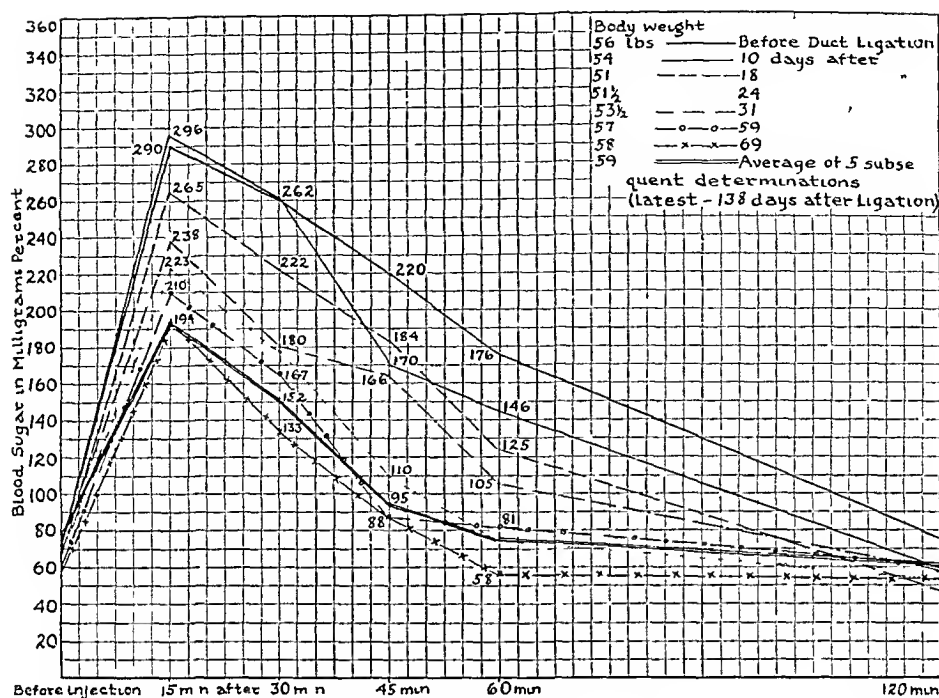


Fig 1 (dog 38) —Curves showing sugar tolerance before and at intervals after ligation of the parotid duct

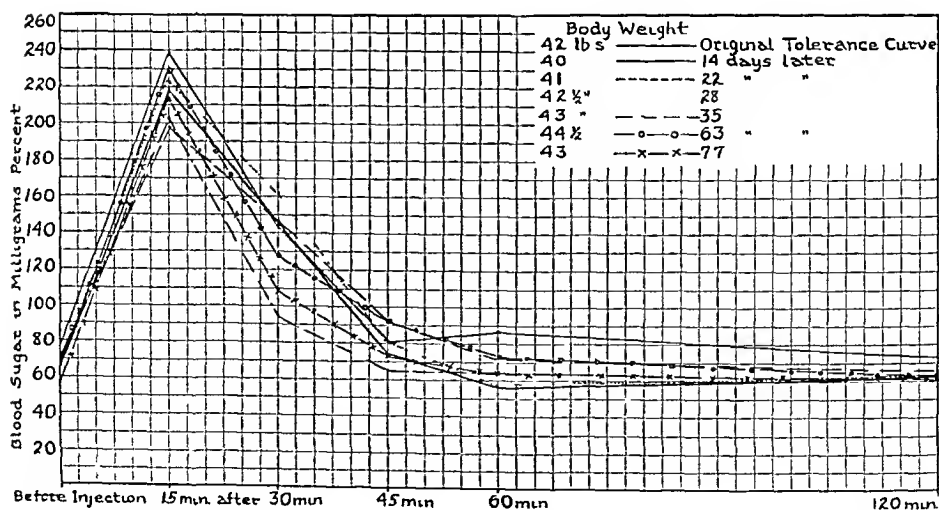


Fig 2 (dog 39) —Control for chart in figure 1 Determination of sugar tolerance in an animal that was not operated on, made in the same manner and at intervals corresponding to those in the preceding chart

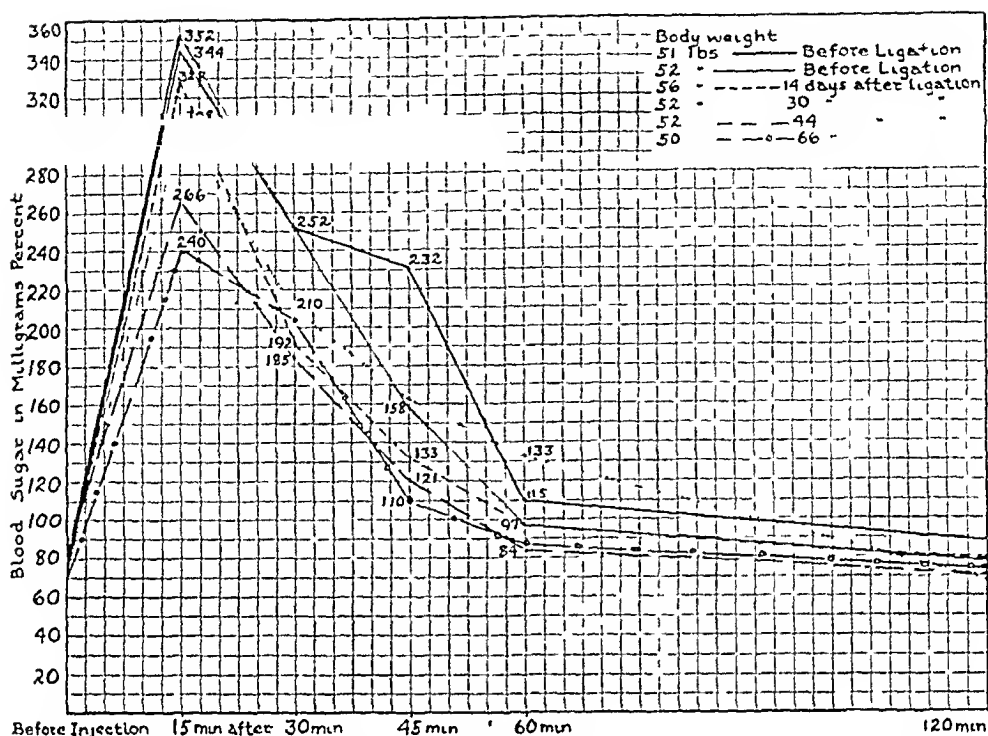


Fig 3 (dog 40) —Effect of ligation of the parotid duct on dextrose tolerance curves

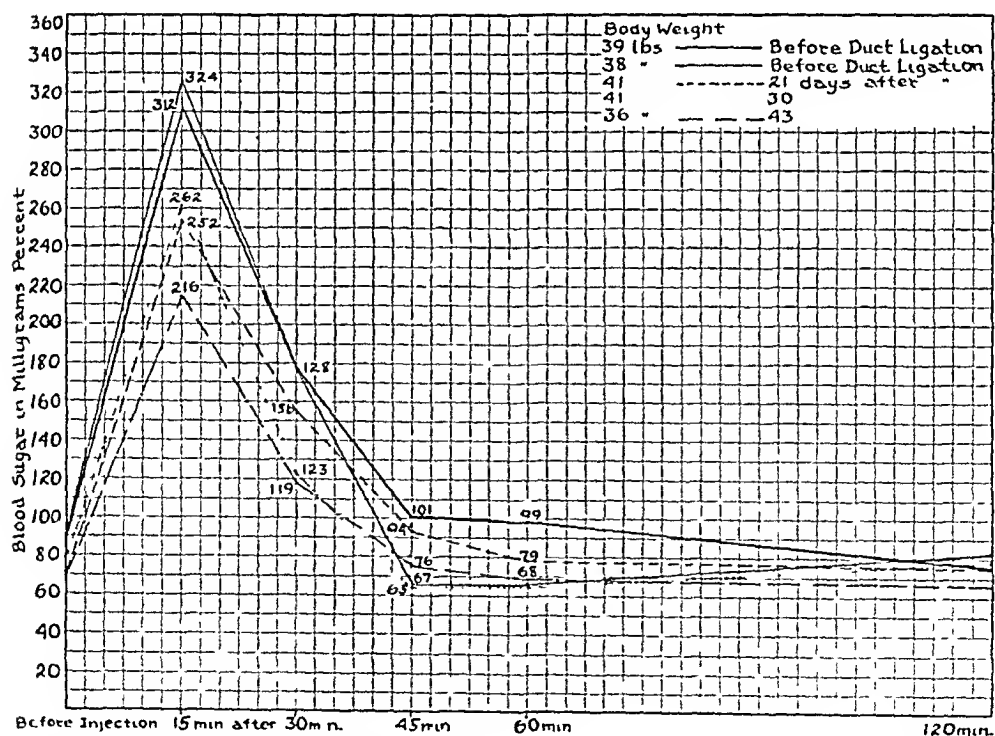


Fig 4 (dog 43) —Tolerance curves, showing dextrose tolerance before and after ligation of the parotid duct

Occasionally an animal is encountered for which it is difficult to attain the usual type of curve and such animals should not be used for these experiments. In our experiments, the dogs were kept on the controlled diet for several weeks before the determinations were begun. They were fed and handled by the same keeper, and his familiarity with them overcame much of the apprehension and excitement of the subsequent determinations. Repeated determinations were made on each animal at the beginning of the experiment. The concentration of the dextrose solution and the time of injection were kept as constant as was possible.

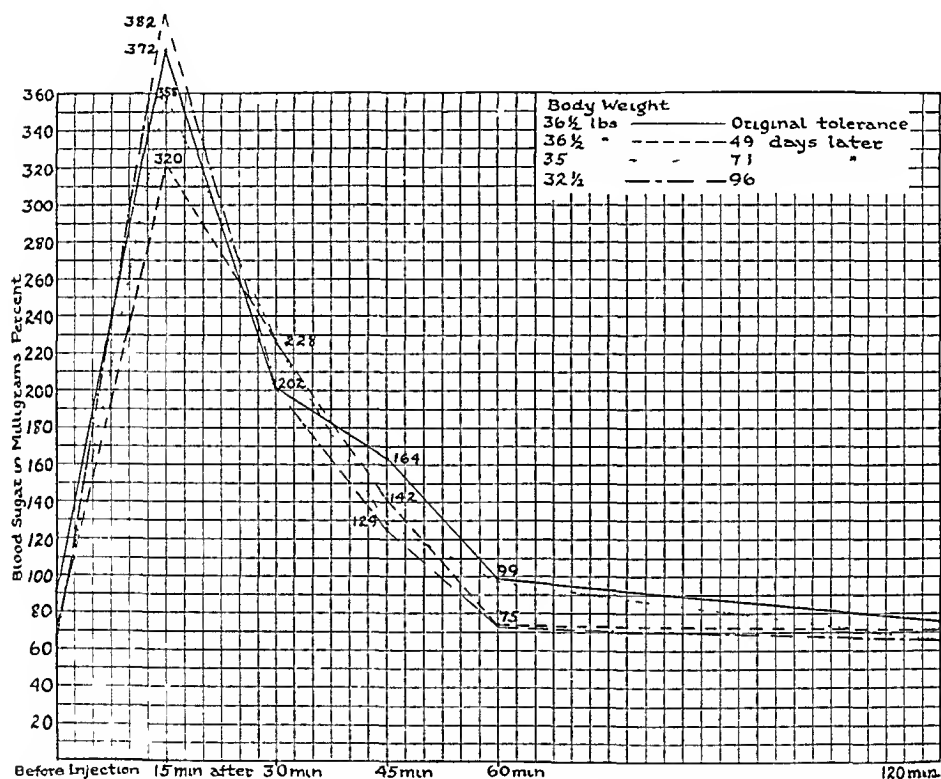


Fig 5 (dog 44) —Control for charts in figures 3 and 4. No similar fall in blood sugar curves is seen in an animal that was not operated on.

The determinations of blood sugar were made by persons entirely unfamiliar with the identity of the animals from which the specimens were taken. Duplicate determinations were made at sufficiently frequent intervals to insure the accuracy of the methods. Two groups of control animals were used, one in which the tolerance studies were repeated at about the same intervals as in the experimental animals and another in which a sham operation was done that involved approximately the same amount of dissection in the same region as in the experimental animals, but in which the parotid ducts were not disturbed.

All surgical operations were done under ether anesthesia, with morphine premedication and with the usual aseptic precautions. Before

the parotid ducts were ligated, the two cheeks were shaved and prepared with tincture of iodine. An incision about three-fourths inch (2 cm) long was made in the line joining the angle of the mouth with the posterior margin of the cartilage of the ear, over the prominent portion of the masseter muscle in the cheek. The masseter muscle was

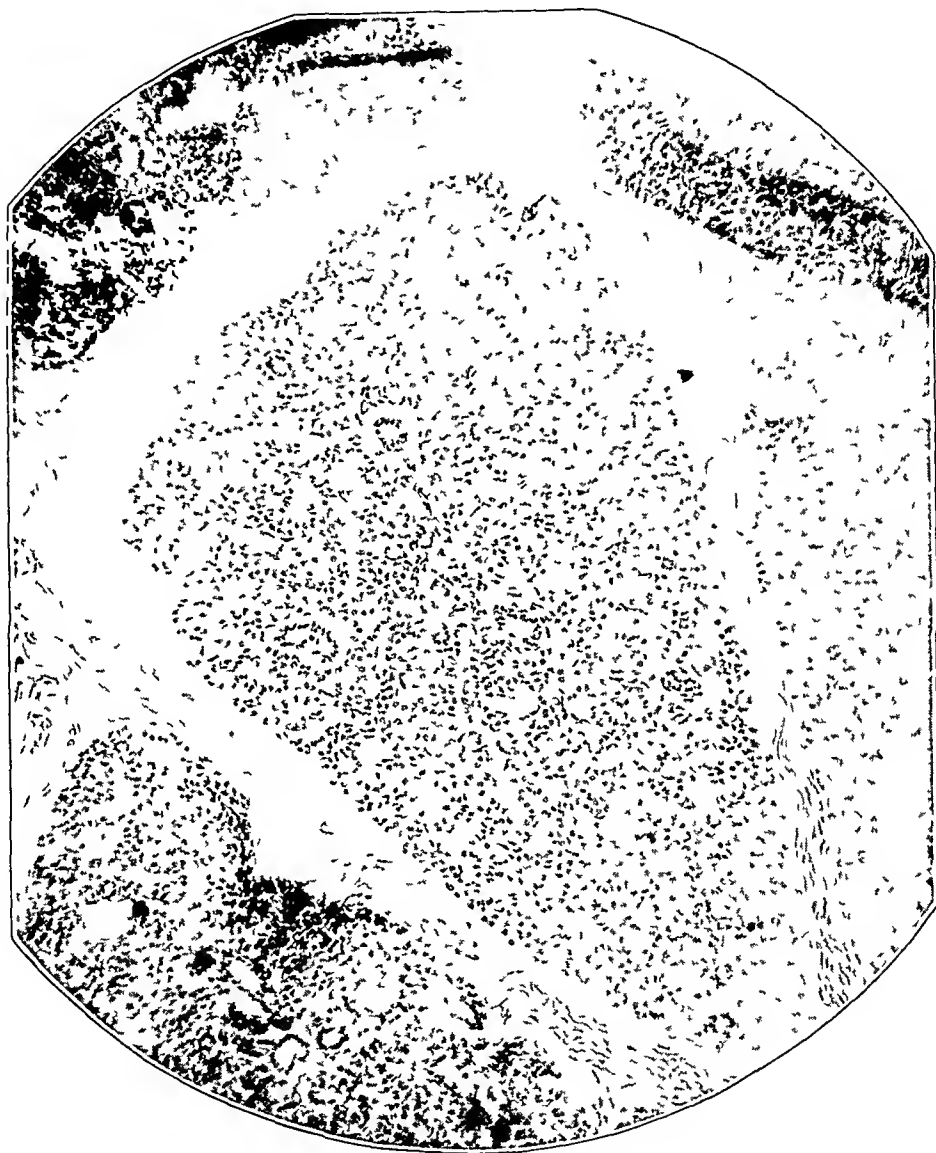


Fig. 6—Photomicrograph of normal dog's parotid gland

exposed, and the duct was readily seen as a fine, translucent, straight structure, lying just beneath the fascia over the muscle, and running in the direction of the muscle fibers. The only structures that might be mistaken for the duct are the branches of the facial nerve. These, however, lie slightly more superficially, are more opaque and less direct in their course and, if followed, are seen to branch or to unite with adjacent branches. The ducts were doubly clamped and ligated with silk,

and the intervening segments, usually about 1 cm long, were excised. If any doubt existed as to the identity of the duct, the segment that had been removed was sectioned. The fascia over the ligated duct was closed with a few interrupted, fine catgut sutures, and the skin was united with an intradermal stitch. As a rule, no dressing was applied

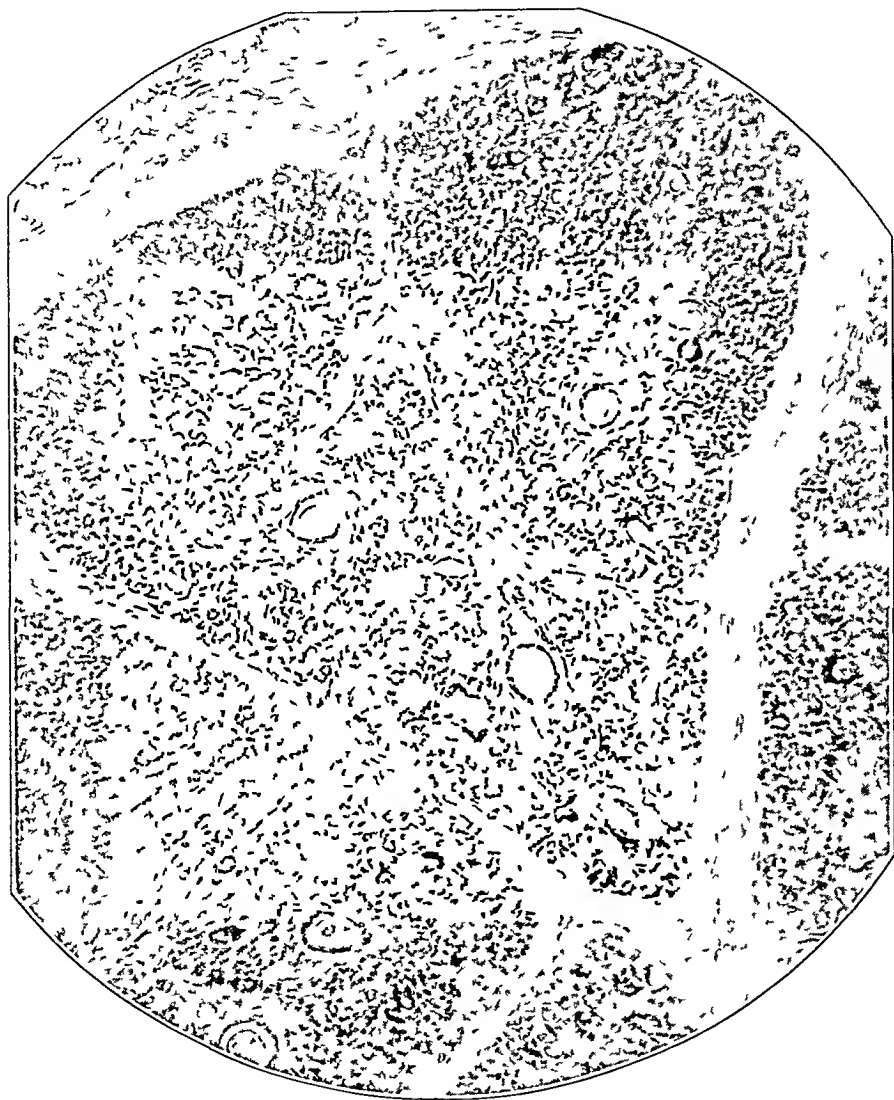


Fig 7—Section of parotid gland thirteen days after ligation of the duct. Note dilatation of secretory ducts.

The animals withstood the operation very well. Marked swelling of the parotid gland was apparent at the end of twenty-four hours, it reached its maximum in from two to three days, and then gradually subsided. In some of the animals the wounds opened, discharging serous secretion. In none were there persisting salivary fistulas. Postoperative determinations of the sugar tolerance were not made until the wounds had entirely healed and the animal seemed to have entirely recovered.

from the operation. During fasting there was no constant change in the blood sugar levels of our animals as a result of the ligation of the parotid ducts. There was, however, a definite increase in the sugar tolerance, as measured by a lower blood sugar curve and by a rapid return to normal levels following the injection of dextrose solutions.

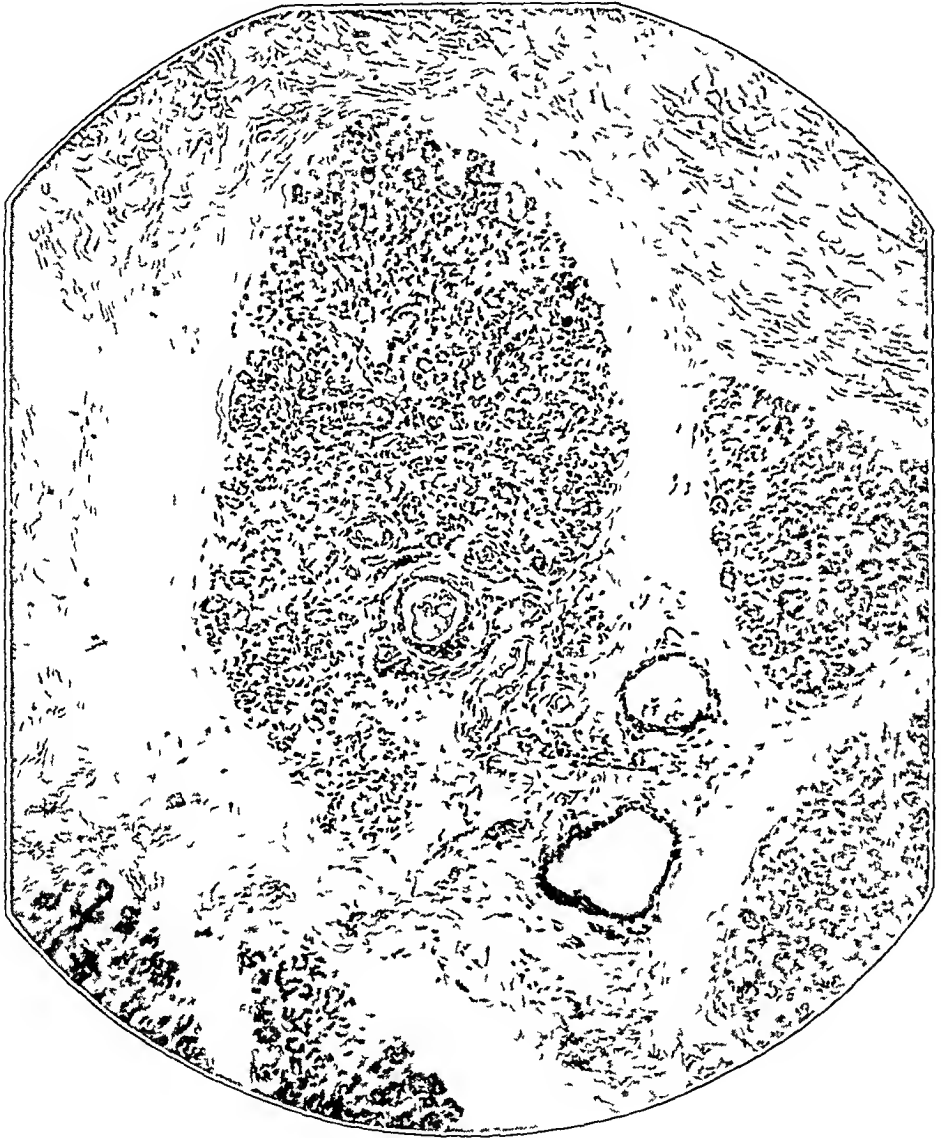


Fig 8—Parotid gland fifty-eight days after ligation of the duct. The secretory ducts are dilated and there are atrophy and fibrosis of the parenchyma.

This is well demonstrated in the charts. The first postoperative determination of sugar tolerance usually showed a curve higher than those before operation. This is to be attributed to the disturbance in metabolism caused by the operation and the anesthetic. Subsequent curves showed a progressive lowering of tolerance, reaching the lowest levels from four to five months after the operation and then remaining con-

stant There were no decided changes in the body weight or in the general condition of the animals

In some of the animals, the ligated glands were subsequently removed in order to determine what effect that would have on the carbohydrate tolerance These experiments were not conclusive In most of the animals, however, there was some increase in the height of the blood

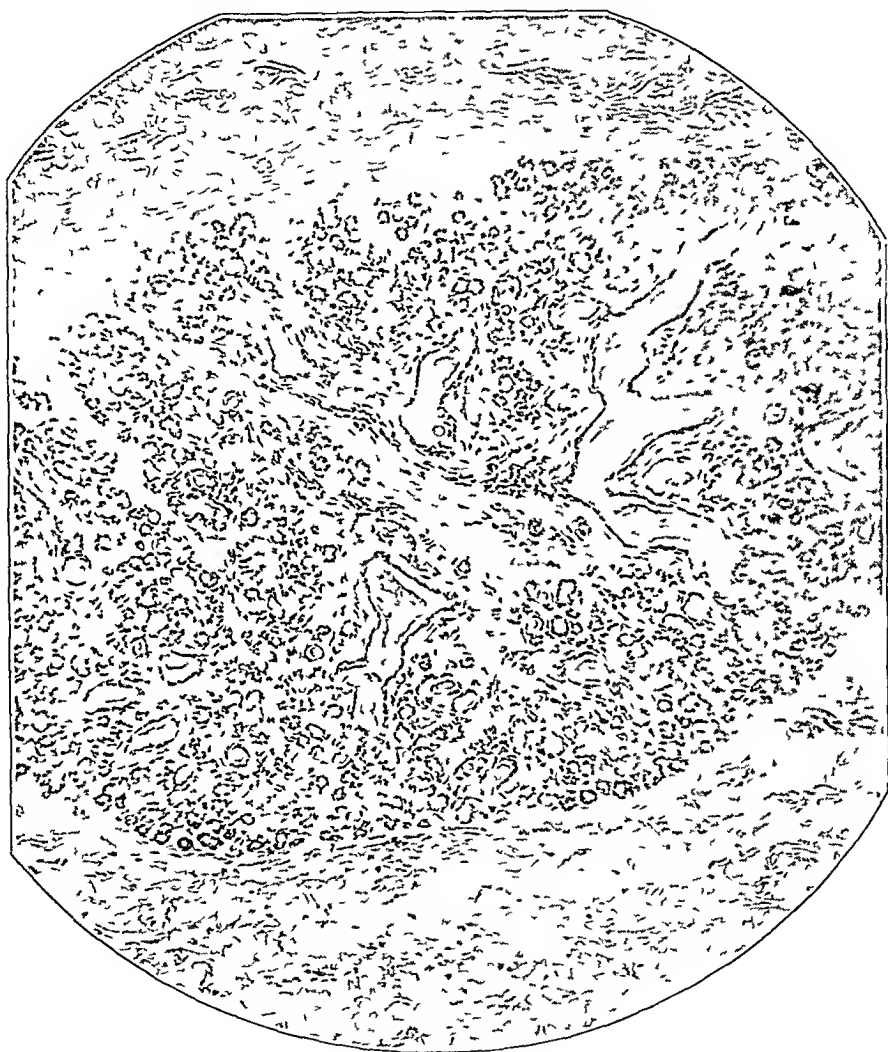


Fig 9—Parotid gland one hundred and thirteen days after ligation of its duct The secretory ducts are greatly distended and there are marked atrophy and cirrhosis of the gland

sugar curve after the removal of the glands The extirpation of the parotid glands could not always be satisfactorily performed These glands in the dog are not sharply circumscribed, but are spread out, being widely distributed in the deep fascia of the face To insure removal of all glandular tissue, it is necessary to make a block dissection of the deep fascia down to the muscles, extending from the zygomatic

ridge above to the masseter muscle anteriorly, the ear posteriorly and the submaxillary gland below. So extensive a dissection requires the sacrifice of nerves and blood vessels, and is attended with considerable postoperative swelling and not infrequently with delayed healing of the wound. Even then one cannot be sure that all traces of glandular tissue have been removed.

Parotid glands were removed at varying intervals after the ligation of their excretory ducts, and the specimens were examined microscopically. Prof. R. R. Bensley, of the department of anatomy of the University of Chicago, studied these preparations. He reported a very slow but gradual dilatation of the salivary ducts, with atrophy and fibrosis of the gland parenchyma. Nowhere did he find evidence of proliferation of the gland or of the development of abnormal types of cells.

COMMENT

The results of these experiments indicate that the parotid glands of the dog exert some influence as yet not recognized on the control of the carbohydrate metabolism. This is of some significance in view of the total ignorance as to the purpose of the salivary glands. As Professor Bensley expressed it, aside from secreting some slipperiness and wetness, they have no known function. Even the well known digestive function is absent in certain species of animals. It has frequently been suggested that perhaps these glands might have an internal secretory action as well as their external secretory one. The frequent association of orchitis and oophoritis with inflammation of the parotid glands in epidemic parotitis has suggested a relationship between the salivary glands and the gonads. The resemblance between the parotids and the pancreas has already been pointed out. Both structures have their origins as ventral out-pouchings from the primary intestine. Both are concerned with the elaboration of digestive enzymes, specifically those of a starch-splitting nature. Pancreatitis occurring during or after epidemic parotitis has been described (Farnam,⁹ Stevens¹⁰), and fatal cases of diabetes have followed mumps (Patrick,¹¹ Gundersen¹²), conversely, hypertrophy and inflammation of the parotid glands have been noted in diabetic patients.

The results of our experiments confirm the findings of Goljanitzki,⁵ Mansfeld⁶ and Seelig.⁷ They indicate a relationship between the sali-

9 Farnam, L. W. Pancreatitis Following Mumps, *Am J M Sc* **163** 859, 1922

10 Stevens, A. M. Mumps of the Pancreas, *Arch Pediat* **42** 333, 1925

11 Patrick, A. Acute Diabetes Following Mumps, *Brit M J* **2** 802, 1924

12 Gundersen, E. Is Diabetes of Infectious Origin? *J Infect Dis* **41** 197 (Sept) 1927

vary glands and the carbohydrate metabolism. The nature of the action is as yet unknown. In a few experiments by Mansfeld, ligation of the parotid ducts was found to be without effect in totally depancreatized animals. These results have been confirmed by Dr. Samuel Saskin and me¹³. This would indicate that the action is not a primary insulin-like one, but rather that it stimulates or activates the pancreas to secretion of insulin. Such an action might well be hypothecated. Just as the saliva stimulates the gastric glands to secrete gastric juice in anticipation of its need, so the salivary glands may stimulate the pancreas to elaborate insulin in anticipation of an increased need consequent on the taking of food. The persistence of the effect after the ligated glands have been removed suggests that possibly an antisubstance has been prevented from reaching the alimentary tract by the ligation of the duct and thus has increased the tolerance. The absence of any proliferative changes in the excised glands and the fact that progressive cirrhosis was the only finding are the strongest arguments against the existence of any positive secretion. Further work is in progress in an attempt to determine some of these facts.

CONCLUSIONS

1 Ligation of the parotid ducts in normal dogs results in an increased dextrose tolerance, as measured by the height of the blood sugar curve following the injection of dextrose solution.

2 Histologic study of parotid glands removed at varying intervals after ligation of their ducts reveals only gradual dilatation of the ducts, with atrophy and fibrosis of the glandular parenchyma.

3 Extirpation of the parotid glands in which the ducts had been ligated produced inconstant effects on the carbohydrate tolerance. Usually there was some increase in the height of the blood sugar curve, but the values rarely returned to the levels that had been maintained before the ducts were ligated.

4 Further work is in progress to determine the source and nature of the relationship between the parotid glands and the carbohydrate metabolism.

13 Zimmerman, Leo, and Saskin, Samuel. Effect of Ligation of the Parotid Duct on the Carbohydrate Tolerance of Totally Depancreatized Dogs, *Arch. Int. Med.*, to be published.

CHOLESTEROL-THORAX IN TUBERCULOSIS (CHOLESTEROL PLEURISY)

REPORT OF A CASE *

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The accumulation of fluid in the pleural cavities is a common condition, a number of interesting types having been encountered, and in all probability the rarest of these is that known as cholesterol pleurisy or sometimes spoken of as cholesterol-thorax. Cholesterol is constantly found in the tissues and is also rather uniformly found in all pleural effusions, but in the latter it is practically always present as an ethereal salt. The majority of writers on this subject agree that the condition should be defined as an effusion that is rich in cholesterol in crystalline form, and further, that the total amount of cholesterol in the effusion may be high or low, the amount not always determining the form in which it is found. In some cases reported the total amount of cholesterol has been high and in others there has been much less, but in all instances one should be able to demonstrate the crystals in great numbers. Thus the microscopic examination of the pleural fluid exhibits the very typical and characteristic crystals which are peculiar to crystalline cholesterol. Textbooks and authorities on diseases of the chest give the condition scant mention and on inquiring among my colleagues I can find no instances in their experiences in which cholesterol pleurisy has been observed. In a search of the literature twenty-one cases have been discovered, and the great majority of these are found in foreign journals, the condition apparently having been given much more attention in other countries than in our own. The first case was said to be reported by Guenau de Mussy, and in 1882 Churton¹ called attention to two cases, one occurring in a man of 38 years who had a bilateral hemorrhagic pleural effusion containing much cholesterol and who subsequently developed an empyema and supposed septicemia. This patient had a history suggestive of a tuberculous infection at the age of 18 years, and at autopsy several suggestive areas were demonstrated in the apex of the left lung, but unfortunately no microscopic studies of this tissue are reported. Another case occurred in a man of 31 years who had a previous pleural effusion and who ultimately died of

* Submitted for publication, June 1, 1931

¹ Read before the American Climatological and Clinical Association, Hot Springs, Va., May 8, 1931

1 Churton, Thomas. Tr. Clin. Soc., London 15 9, 1882

cirrhosis of the liver, the autopsy showing no tuberculosis. In 1907 Hedestrum published the report of a case of this condition, and in 1908 Ruppert² and Hess reported cases. Caussade described a case in 1914 in a man of 27 years who had previously had a pleural effusion that was probably tuberculous. In 1917 Schulman³ observed a man of 62 years who had also had a previous pleural effusion, and in the same year Arnell⁴ reported on this condition. In 1918 Weems⁵ reported the case of a patient who had had a previous pleural effusion, and it was his opinion that the condition of cholesterol pleurisy was probably associated with faulty cholesterol metabolism, his patient having a definite increase in blood cholesterol.

In 1919 Izar⁶ and Sharpe⁷ published instances of cholesterol pleurisy, the latter citing two cases, one of which was definitely associated with tuberculosis. The other case occurred in a boy of 9 years who probably had a pleural tuberculosis.

Other cases were reported in 1924 by Stockman⁸ and Ceyon,⁹ the patients in the latter's two cases both having tuberculosis. Mainini¹⁰ described two cases in 1925, both patients having tuberculosis. Rouillard and Nativelle,¹¹ in 1927, told of a case occurring in a woman who had had a pleural effusion twenty-one years previously.

In making an effort to analyze these reports, one is immediately impressed with the frequency with which tuberculous infection is encountered in patients having cholesterol-thorax. In a considerable number of instances these patients have definite pulmonary tuberculosis, and in the majority of cases a history of previous pleural effusion is noted which was apparently primary in origin, and in the light of present-day thinking would be looked on as being probably tuberculous. It is striking also to note that these effusions occurred frequently many years before the patient was seen with cholesterol-thorax. With the exception of one case in a child of 9 years, reported by Sharpe, all of the other patients were adults and many of them beyond the fourth decade of life. Only a very few of the patients were women. It goes without saying that apparently the condition follows a chronic

2 Ruppert. *Munchen med Wchnschr* **55** 510, 1908.

3 Schulman, M. *Pleural Effusion*, *J A M A* **68** 1256 (April 28) 1917.

4 Arnell, P. *Hygiea* **79** 737, 1917.

5 Weems, B. F. *Am J M Sc* **156** 20, 1918.

6 Izar. *Riforma med* **35** 961, 1919.

7 Sharpe, H. *Brit M J* **2** 462 (Oct 11) 1919.

8 Stockman, J. *Paris Theses*, 1924.

9 Ceyon, A., Fiessinger, N., and Meignan, P. *Bull et mem Soc med d hôp de Paris* **48** 943 (June) 1924.

10 Mainini, C. *Bull et mem Soc med d hôp de Paris* **49** 1534 (Dec) 1925.

11 Rouillard, J., and Nativelle. *Bull et mem Soc med d hôp de Paris* **51** 1717 (Jan) 1927.

pleural inflammation, the type of the preceding inflammatory fluid being invariably serofibrinous or hemorrhagic

Clinically, the disease must be looked on as chronic, usually not fatal in itself, and manifested by cough, dyspnea, very little if any expectoration and practically no constitutional symptoms such as fever, rapid pulse and toxemia. When postmortem material could be studied, the changes were invariably those of a long-standing chronic condition with much thickening of the pleurae, and in some instances calcification had ensued. When chemical determinations of the blood have been made, there seems to be no constancy as to the cholesterol values noted in the blood of these patients. Not many instances of complications were encountered, although rupture of the fluid into a bronchus might occur, and in some of the cases observed the fluid became purulent, but the question of frequent punctures in order to relieve pressure might have entered into this in the way of secondary infection. The diagnosis of the condition is made entirely by aspiration of the chest on the basis of physical findings, indicating the presence of fluid in one or both pleural cavities. When aspirated, this fluid might be found to be brownish, sometimes yellow or dirty white, and it is usually thin. It has a satin-like appearance, and grossly one can note the presence of a sheeny material in suspension. The specific gravity of the fluid has a wide range. It usually does not contain organisms, and microscopic examination shows myriads of cholesterol crystals in their very typical form. In none of the reports is any mention made as to the demonstration of tubercle bacilli in this fluid.

As for treatment, it seems that some cases would probably not need any, but the symptoms are usually those of respiratory embarrassment and frequent aspirations of the fluid would be the correct procedure. Surgical measures should not be considered unless invasion of the fluid with micro-organisms occur.

The following case is cited from the private medical service at the University Hospital, Baltimore

REPORT OF A CASE

History—This history was obtained from relatives and in part from the patient G. A., a man, white, complained of headache, dizziness, vomiting and fever of ten days' duration. The family history was not significant. For many years the patient had been prone to take "cold" easily, and about two weeks before admission to the hospital, just before the beginning of the present illness, he had an attack of "grip." At the age of 20 years he had an illness which was said to be pneumonia, and since that time he had had cough and bronchitis every winter, the cough being most noticeable in the morning and accompanied by a yellowish sputum. After his attack of pneumonia, he stated that the doctor aspirated some fluid from the left side of his chest on one occasion, but he did not remember any further details although he was sick at that time for a number of weeks. Seven

years before the present illness he had an attack of severe pain in the region of the left kidney, which occurred off and on for several weeks, but there was no definite diagnosis made as to the condition then. There was no history of venereal disease. The patient's habits were not unusual.

The patient was admitted to the University Hospital on Jan 22, 1930, complaining of headache, vomiting and some "gas on the stomach" for the past ten days. His wife stated that he had been irrational for the past forty-eight hours. His headaches had been persistent, his temperature has ranged from normal to 101.5 F, and he had had several chills.

According to the pulmonary history, there had been rather constant shortness of breath on exertion. Fifteen pounds (6.8 Kg) in weight had been lost in the last year. The gastro-intestinal history was not important. The cardiovascular, renal history, genito-urinary history and history of the special senses showed a normal condition.

Physical Examination—Jan 23, 1930. Physical examination showed a white man, aged 45, who resisted examination and was disoriented, he looked quite ill, and there was evidence of undernutrition.

The head was entirely normal except for slight redness of the throat.

Except for slight rigidity, the neck was normal.

Examination of the heart and blood pressure showed nothing unusual. The lungs were normal except that on the left side the percussion note was impaired in the entire axillary space from the apex to the base and from the fourth rib in front down to the base, impairment blending with cardiac dullness. Posteriorly, the percussion note was impaired from the angle of the scapula to the base and was perfectly flat. The breath sounds over the left part of the back, except at the extreme apex, were absent. The base of the right lung descended well on deep inspiration.

The spine and abdomen were normal.

The reflexes of the extremities were all present and normal. There was no evidence of paralysis.

Otherwise, the results of the physical examination were negative.

Laboratory Reports—The urine was normal except for the fact that on several occasions a trace of albumin was noted.

The blood was normal morphologically. Cultures were negative. Chemical examination showed 74 mg of cholesterol (whole blood) per hundred cubic centimeters. The Wassermann reaction was negative.

On January 22, the spinal fluid came out under a slight increase of pressure, increased by compression of the jugular vein, it was cloudy, contained 4 plus globulin and 348 cells per cubic millimeter. Practically all the cells were lymphocytes. The colloidal gold curve was 0134344321.

On January 24, the spinal fluid was unchanged except for an increase of cloudiness and the finding of 820 cells per cubic millimeter. In neither one of the two specimens of spinal fluid were organisms of any sort demonstrated. The predominant cell was a lymphocyte. Cultures made from the spinal fluid were entirely negative, and cultures made on special potato mediums did not grow tubercle bacilli. There was 23 mg of spinal fluid sugar per hundred cubic centimeters.

Exploratory Thoracentesis—January 23. Exploratory puncture was made in the seventh intercostal space on the left side posteriorly, and considerable resistance was met with in the entrance of the needle through the pleura, giving one the feeling of a very hard, thick pleura. A dirty white, milky fluid was obtained. It did not have any odor and when shaken in a test tube looked very much like thin

milk The fluid showed no pus cells or organisms and contained no fat Myriads of typical cholesterol crystals occupied the entire microscopic field

The specific gravity was 1.024, water, 80 per cent

The cholesterol content was 2,353 mg per hundred cubic centimeters of the fluid

No organisms could be demonstrated by direct smear Tubercle bacilli were especially sought but none found Later, all cultures made from the fluid proved to be negative



Fig 1—Roentgenogram of the chest The abnormal shadows on the left side are due to calcification of the pleura and fluid

Pathologist's Report on Guinea-Pigs' Inoculation January 29 Pigs were inoculated with a specimen of the spinal fluid

March 20 Postmortem examination of the pigs showed disseminated tuberculosis

Radiologic Examination (by Dr H J Walton) —January 24 Roentgen examination of the chest showed a very dense, partially calcified shadow in the axillary region and base of the left lung The shadow appeared to lie close to the chest wall and surrounded the lung The mass obscured the detail of the lung The upper portion of the lung above and to the mesial side of this shadow was clear and well aerated The entire right lung was clear There was also a slight calcification in the axillary region of the right base about 1 inch above the diaphragm

The heart was of medium size, and was slightly displaced to the right side. The aorta was normal in width.

The impression was that there was extensive calcification of the pleura surrounding the lower axillary areas of the left lung and beginning calcification of the pleura in the axillary region of the base of the right lung.

The gastro-intestinal tract was normal.

Final Note—January 30 It is believed from the history that the patient had some type of pleural effusion at the age of 20 years that had become cholesterol-



Fig 2—Lung specimen showing thickened calcified pleura and large cavity (held open by glass rods) which contained cholesterol

ized. One might assume that he possibly had a pleural effusion long ago that was tuberculous in origin, and it is most interesting to note that the cause of the patient's death was tuberculous meningitis. It has been noted before that tuberculosis is an invariable finding in cases of cholesterol-thorax.

The final diagnosis was tuberculous meningitis and cholesterol-thorax.

Abstract—Autopsy was performed by Dr W C Merkel, of the department of pathology, University of Maryland.

The body was that of a well developed, though somewhat emaciated, white man. The external examination gave negative results. The peritoneum and abdominal organs as examined in situ appeared normal.

On removing the sternum, it was found that both pleural cavities were obliterated. On the right side, the lung was bound to the chest wall by dense fibrous adhesions. The right lung was voluminous, heavy and purplish red. Throughout this lung there were small granular areas of consolidation.

The left pleural sac presented an unusual picture. The left lung was much compressed and pushed upward and toward the midline. The parietal pleura at the base and about the sides of the pleural cavity and the visceral pleura over the anterior, lateral and posterior surfaces of the lung were thick and rigid. By careful dissection, the lung and thickened pleural sac were removed en masse. A study of the specimen showed the lung compressed about the large bronchi. On the surface of the lung there was attached a boxlike mass which assumed the shape of the cavity from which it had been removed.

This mass was extremely hard, it measured 23 cm from apex to base, 24 cm across its convex anterolateral surface at its widest portion and about 14 cm in its greatest anteroposterior dimension. The wall was hard and gritty, it was cut through with the aid of a bone saw. On section, it was found that this mass was a closed cavity containing about 1,400 cc of a milky fluid in which shimmering particles were seen. The wall was irregular, varying from 6 mm to 2 cm in thickness, it was composed of hyalinized fibrous tissue and contained masses of calcareous material and spicules of bone. In the thickened visceral pleura near the apex of the lung, there was a fibrocaseous nodule which measured about 1 cm in diameter.

The brain showed a moderate injection of the vessels of the pia-arachnoid with some slight thickening of the leptomeninges. Typical tubercles embedded in a tuberculous granulation tissue involved the leptomeninges. No tubercles were found in the brain tissue.

A study of the other organs revealed little of interest. There was no evidence of tuberculosis except in the pleura and in the meninges.

Anatomic Diagnosis—The anatomic diagnosis was fibrocaseous tubercle of the visceral pleura, near the apex of the left lung, tuberculous meningitis, fibrosis, calcification and ossification of visceral and parietal pleura of the left lung, "cholesterol-thorax" of the left lung, partial atelectasis of the left lung, acute bronchopneumonia of the right lung, old pleural adhesions of the right lung, and moderate generalized arteriosclerosis.

COMMENT

1 The case report is that of cholesterol pleurisy occurring in a man who had a previous history of pleural effusion following pneumonia. I venture the opinion that in the absence of a clearer history it might be that the condition was originally one of tuberculous pleurisy with effusion and not of pneumonia. It is interesting to note that this patient actually did have tuberculosis involving the central nervous system many years after his probably tuberculous pleurisy, and that there was also autopsy evidence of a tuberculosis of the pleurae.

2 Cholesterol-thorax might be looked on in the majority of instances as an unusual end-result of a long-standing pleural effusion which was originally tuberculous in origin. One might assume that in view of the fact that the majority of primary pleural effusions are tuberculous in origin the condition of cholesterol-thorax simply means that an

old tuberculous effusion that has not been cured and has not caused death will in some instances eventually become cholesterolized

3 The question of cholesterol metabolism is, of course, as yet an unsolved problem, and it may be possible that the only cases in which an old pleurisy becomes cholesterolized is in persons who have an abnormal cholesterol chemistry, this observation, of course, being theoretical

In pulmonary tuberculosis, the reports vary as to the cholesterol chemistry, and it would seem that the cholesterol content in the blood in tuberculous infections may be increased or decreased Eichelberger and McCluskey¹² claim that a rising or stationary hypercholesterolemia indicates immunity and resistance, while a falling blood cholesterol or a low blood cholesterol indicates a lowering in the immunity and resistance

12 Eichelberger, L., and McCluskey, K. L. Chemical Studies in Tuberculosis I Plasma Proteins, Cholesterol and Corpuscle Volume, Arch Int Med **40** 831 (Dec) 1927

CARCINOMA OF THE GASTROJEJUNAL STOMA FOLLOWING OPERATION FOR PEPTIC ULCER *

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CHICAGO

Since gastro-enterostomy came into general use in the treatment for peptic ulcer and its complications, certain nosologic entities previously practically unknown have loomed into prominence. Gastrojejunal ulcer, a unique and unimportant lesion prior to the era of gastro-enterostomy, is now accorded a great deal of space in treatises on peptic ulcer. High intestinal obstruction accompanied by symptoms of a vicious cycle evoked little attention until the universal adoption of gastro-enterostomy, after which an enormous literature appeared on the subject. To these more common sequelae of the anastomosis can be added carcinoma of the stoma, an extremely rare but interesting condition.

The occurrence of a malignant growth at the site of a gastrojejunal anastomosis was mentioned by Schwarz¹ in a paper dealing with observations at operation in gastro-enterostomized persons. The author gave an account of a patient who had an anterior gastro-enterostomy performed in 1909 for pyloric ulcer. The patient felt well for about six years, after which he began to lose weight and to vomit. Laparotomy disclosed a huge dilatation of the proximal loop and collapse of the distal loop. The cause of obstruction, according to Schwarz, was a carcinoma of the gastro-enterostomy ring. Metastases to adjacent lymph glands and to the peritoneum were also noted. A Braun anastomosis was performed and was followed by rapid improvement. The patient was convalescing at the time the report was rendered, and no subsequent communication has appeared. A second instance of carcinoma in the line of union of the stomach and jejunum was mentioned by Hurst and Stewart,² without any accompanying clinical history or description.

A third case was reported rather recently by Eichelter³. A man of 55 had a partial gastrectomy (Billroth II) performed for chronic penetrating

* Submitted for publication, June 25, 1931.

* From the Department of Medicine of the University of Illinois College of Medicine and the Department of Pathology of the Cook County Hospital.

1 Schwarz, in discussion of Lengemann. *Operationsbefunde an Gastroenterostomierten*, *Zentralbl f Chir* **53** 3000 (Nov 20) 1926.

2 Hurst, A. F., and Stewart, M. J. *Gastric and Duodenal Ulcer*, London, Oxford University Press, 1929, p. 429.

3 Eichelter, G. *Spontanperforation des paralytisch erweiterten Duodenal-Schenkels 4 Jahre nach subtotaler Magenresektion wegen Ulcus (primares Karzinom an der Anastomosenstelle)*, *Deutsche Ztschr f Chir* **222** 106, 1930.

ulcer. He remained well for three and one-half years, then abdominal symptoms reappeared. When he came under the observation of Eichelter, at the age of 59, he was suffering from symptoms of a perforative peritonitis. Operation disclosed a nodular tumor at the anastomosis, dilatation of the proximal loop and acute rupture of a distention ulcer in the duodenum. Duodenojejunostomy and jejunostomy were performed. Shortly thereafter the patient died. Autopsy showed the gastro-enterostomy stoma to be narrowed by a firm, infiltrative growth, which microscopically proved to be an adenocarcinoma. The mucosa in the region of the anastomosis showed thickened folds and tumor formation. One of the mucosal swellings projected into the narrowed mouth of the proximal loop. Several metastases were found in the liver and esophagus and in a few peripancreatic lymph glands. The diagnosis of simple ulcer made at the time of the original operation in 1925 was confirmed by further study of the previously resected lesion. Eichelter concluded that the carcinoma had its point of origin in the anastomosis.

A fourth case, which constitutes the basis of this communication, presents a number of interesting features that appear to warrant a rather detailed report.

REPORT OF CASE

J. W., a white man of 52, entered the Cook County Hospital for the first time on March 14, 1929, with gastro-intestinal complaints ascribed to a suspected gastro-jejunal ulcer. He related that he had suffered periodically from epigastric distress and heartburn from 1900 until the early part of 1918, when an appendectomy was performed. No relief followed. In June of the same year, he consulted and was operated on by Dr. N. M. Percy, who gave me a complete operative report. The laparotomy disclosed a duodenal ulcer, a chronic cholecystitis and extensive perigastric adhesions. The operative procedures included pylorotomy, with posterior gastro-enterostomy, cholecystectomy and division of the adhesions. For a year following laparotomy, the patient felt entirely relieved of his previous symptoms. After this time, he began to suffer from a recurrence, which led him to attend a dispensary, where he was treated at irregular intervals, with indifferent results.

At the time of entrance into the hospital, postprandial pain, bloating, acid eructations and an occasional attack of vomiting were the presenting complaints. The physical examination disclosed nothing of value. An Ewald meal returned no free acidity and 13 degrees of combined acidity. The test for occult blood on the gastric contents was positive. The chemical test for blood in the stool, which proved positive prior to treatment, subsequently became negative. The roentgenologic report indicated a well functioning gastro-enterostomy, with no evidence of ulcer. On Sippy management, the patient improved greatly but continued to belch. He was discharged on April 1, 1929, and immediately returned to his usual occupation.

The patient was not heard from until Oct. 7, 1929, when he reentered the hospital on account of severe lumbar pain and systemic manifestations of sepsis. An osteomyelitis involving the twelfth dorsal and first lumbar vertebrae was demonstrated and a soft parts abscess subsequently incised and drained. After recovering from the lumbar abscess, the patient directed attention to his gastro-intestinal complaints. He stated that following discharge from the hospital in April, 1929, he remained fairly comfortable for from three to four months. After this period,

his former epigastric burning reappeared one hour after meals. As time went on, the interval between food-taking and the occurrence of distress became shorter and shorter until at the time of his second admission it was usually less than fifteen minutes. Alkalis afforded but partial relief.

Physical examination disclosed, in addition to a considerable loss in weight, an egg-sized, circumscribed mass located in the epigastrium. The mass moved with respiration and was not tender. Repeated Ewald meals yielded no free acid and a total that varied between 6 and 10 degrees. The maximum quantity of material regained by aspiration was 60 cc. The test for occult blood on both the gastric contents and the stool was persistently positive. A roentgen examination made on Oct. 29, 1929, showed a filling defect on the greater curvature in the distal third of the stomach, and a gastro-enterostomy stoma that functioned moderately well.



Fig 1—Roentgenogram showing the filling defect on the greater curvature side of the distal third of the stomach.

The roentgenologist, Dr. C. H. Warfield, suggested the diagnosis of carcinoma of the gastrojejunal stoma.

The patient continued to suffer from postprandial epigastric burning, which was consistently aggravated by alkalis. Hydrochloric acid afforded some amelioration. In addition to the burning, the patient complained of a hunger pain, which occurred before meals and at night and was generally relieved by food. Two additional roentgen examinations demonstrated the same defect (fig. 1) that had been noted previously. The distress increased in intensity and persistency until the patient finally consented to submit to an operation. Accordingly, on Feb. 6, 1930, a laparotomy was performed by Dr. R. W. McNealy. There was evidence of a previous pylorectomy and posterior gastro-enterostomy. In the region of the anastomosis a soft, irregular mass was felt. There were no enlarged glands in the vicinity and

no demonstrable tumor nodules in the liver. The enterostomy was unhooked and the portion of stomach containing the tumor mass resected. The defect in the jejunum was then united to the lower end of the gastric opening (Billroth II). Following operation, the patient vomited fresh and clotted blood. A blood transfusion and coagulants failed to check the hemorrhage, and on Feb 8, 1930, two days after operation, the patient died. Permission for autopsy was not granted.

Gross Description of Tumor—The specimen consisted of a resected sleeve-like portion of the stomach that measured 3 and 6 cm along the lesser and greater curvatures, respectively. The distal end had been long since surgically closed. The diameter of the proximal opening was 8 cm. The mucosa in the region of the

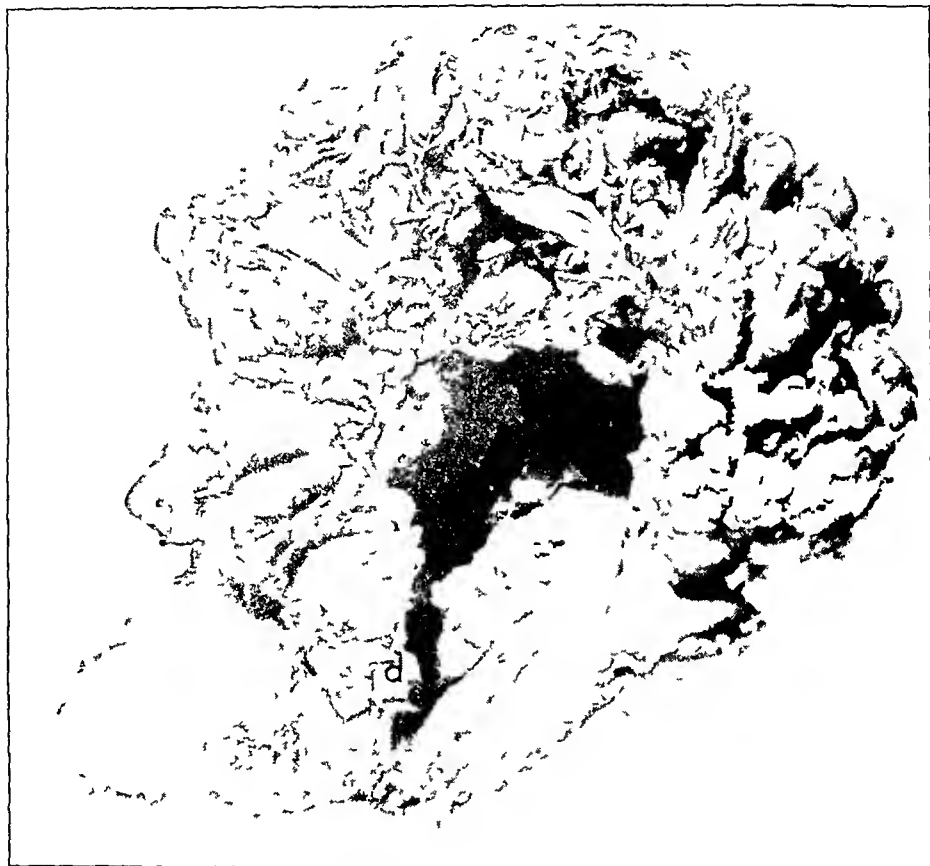


Fig 2—Polypoid tumor involving approximately three fourths of the circumference of the gastrojejunal stoma (seen from the gastric side). The histologic material for figure 3 was obtained from the right border of the defect (*d*)

proximal opening was relatively normal. In approaching the gastro-enterostomy, the mucosa was seen to be thickened and somewhat mammillated. Occupying the region of the distal stoma was a polypoid mass (fig 2), which apparently had its point of origin in the margin and encircled about three fourths of the opening. The tumor was crescentic in form, the widest portion being near the greater curvature side, where it measured 6 cm. The narrowest portion of the tumor was located near the lesser curvature, in the region of which it possessed a width of 2 cm. The tumor consisted of closely set polyps of approximately uniform length but of variable thickness. The polyps that projected from 1.5 to 2 cm above the surface of the surrounding mucosa were from 2 or 3 mm to 2 cm thick. The thin polyps had slender pedicles whereas the thicker polyps were for the most part sessile.

Cross-section of the gastric wall permitted differentiation of the individual coats. The mucosa exhibited a moderate thickening and demonstrated polypoid projections composed of a relatively homogeneous, white tumor tissue. The submucous layers were unchanged except for moderate thickening of the muscular coat. In the region of the lesser curvature was a strip of tissue 3 cm broad which was free from the aforementioned luxuriant pediculated growth. The mucosa here, however, was not smooth, but presented discrete, oval and round elevations, from 3 to 8 mm in diameter, projecting from 2 to 4 mm above the surface of the normal mucosa.

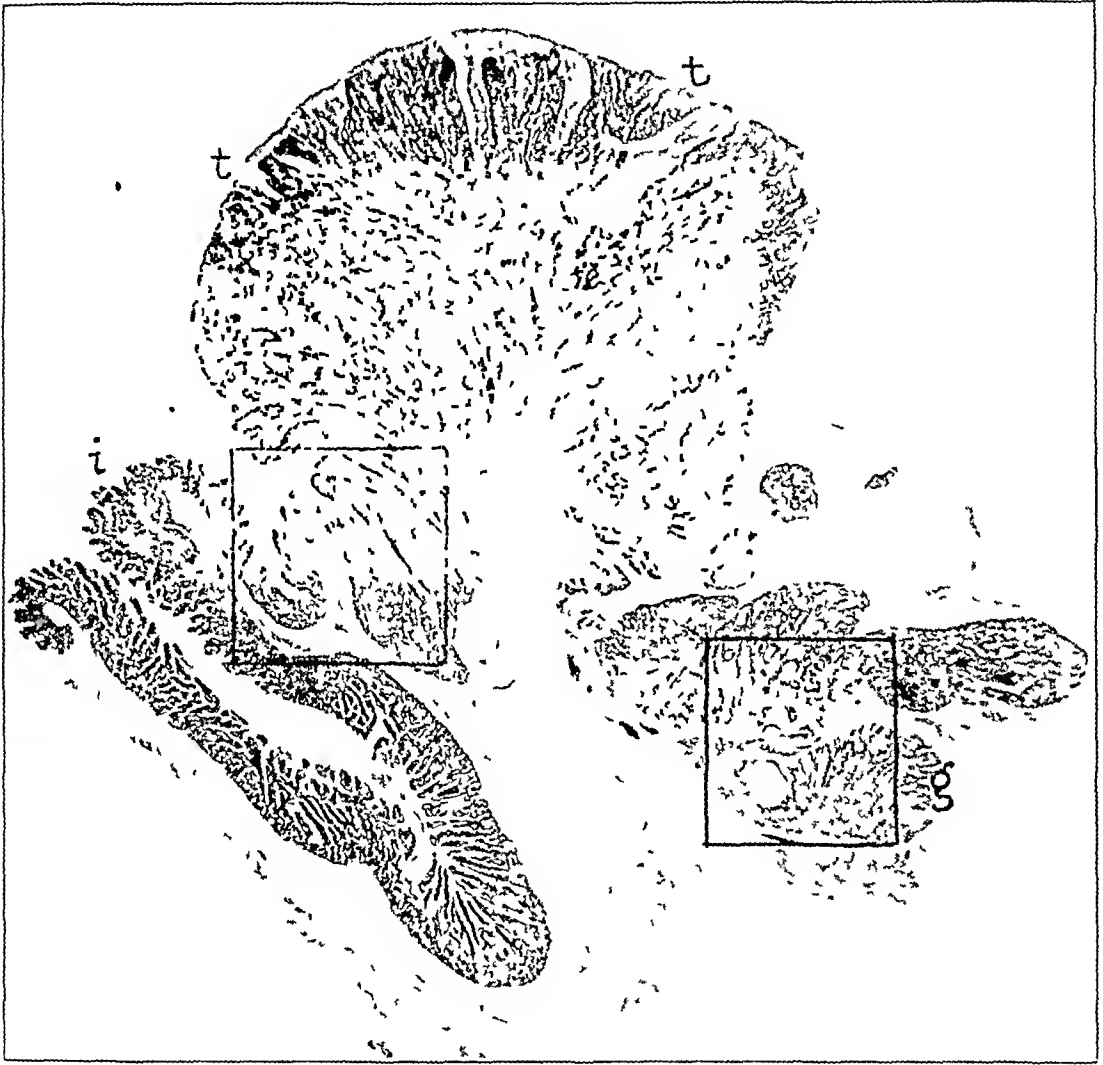


Fig 3—A section taken radial to the axis of the stoma to include intestinal mucous membrane (*i*), tumor tissue (*t*) and gastric wall (*g*), $\times 7$

Cross-section of the gastric wall in this region showed the excrescences to be sessile, mushroom-like thickenings of the mucosa without extension into the subjacent layers.

Microscopic Report—The most informative sections were the radial ones taken through the ring of polypoid tumor tissue to include parts of the adjoining jejunal and gastric walls (fig 3). On the intestinal side, the mucous membrane was thrown into delicate folds (*valvulae conniventes*), which exhibited the characteristic crypts of Lieberkuhn, containing numerous goblet cells (fig 4). Except for an increased

number of cellular elements in the tunica propria, no significant abnormality of the intestinal mucosa was noted

In approaching the polypoid overgrowth there was a rather abrupt transition (fig 4) from the relatively normal intestinal mucous membrane to an atypical papillary structure, which presented the characteristics of a neoplasm. The newly formed tissue (fig 5) consisted mainly of acini, which were irregular in size, form and arrangement. The glands were generally lined by a single layer of columnar epithelium having no specific characteristics. In places, the lining cells assumed a



Fig 4—A higher magnification of the region indicated in figure 3 to demonstrate the transition from a relatively normal intestinal type to a neoplastic type of tissue, $\times 35$

cuboidal form. There was a lack of uniformity in the relationship of the epithelial cells to one another. A moderate variation in size, shape, polarity and chromatin content of the individual cells was noted. Mitotic figures were encountered rather frequently. The lumina of the atypical glands contained varying quantities of precipitated albumin and cellular elements, including macrophages filled with lipid droplets, polymorphonuclear leukocytes and round cells. The interglandular supportive tissue was edematous and densely infiltrated by cells similar to those noted within the acini. In some areas, the lipophages were extremely numerous, whereas

in other areas the accumulations of polymorphonuclear leukocytes were particularly thick

The transition from the papillary growth described to the nonneoplastic gastric mucous membrane (fig 6) was a gradual one. In approaching the latter, there was encountered a zone in which the glands in the deeper layers were gastric in type and typical in character, whereas those in the superficial layers were indifferent in type and atypical in character. In passing further, the glands that were of the

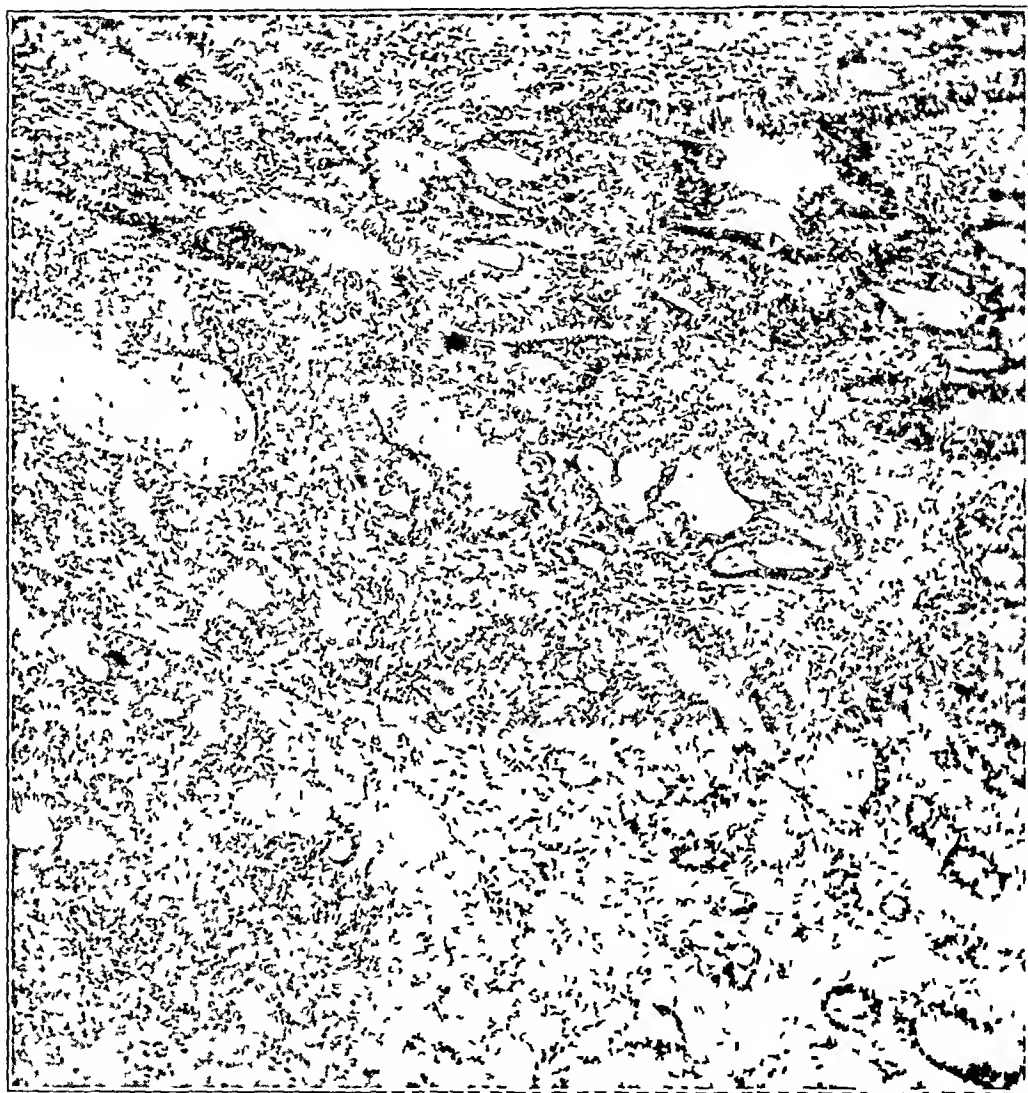


Fig 5—A higher magnification of an area in the polypoid tumor (fig 3 *t*), illustrating the anaplastic character of the growth, $\times 80$

pyloric type assumed a relatively normal appearance, except for cystic dilatations and minor distortions. In the tunica propria of this area there were dense infiltrations of round cells and macrophages. Sections from different portions of the tumor exhibited essentially the characteristics described. However, in some areas, the papillary nature of the growth was much more pronounced than in the portion illustrated in figure 3. There was also a wide variation in the number of polymorphonuclear neutrophils present, for in some sections the leukocytes were densely accumulated whereas in others there were few.

In sections from the flat papillomas located near the stoma, different types of proliferated glands were noted. In some preparations, the glandular structures were of normal appearance, whereas in others the neoplastic character described in connection with the polypoid overgrowth was noted. Transitions between the two kinds of glands were commonly encountered. For instance, in the same section one found crypts and tubules that were relatively normal in appearance and others that were somewhat irregular and bizarre in configuration. The cells lining the



Fig 6—A higher magnification of the transition zone (indicated in fig 3) between gastric mucous membrane, the seat of a catarrhal inflammation, and the adenocarcinoma, $\times 35$

atypical structures were frequently polymorphous and possessed hyperchromatic nuclei. The degree of anaplasia of these crypts and tubules was insufficient to justify an unqualified diagnosis of carcinoma, as infiltrative and destructive properties were not demonstrable. However, the lack of uniformity and the atypical appearance of the glands and individual cells suggested a "precanceromatous" state. Each of these papillomatous nodules appeared to constitute an independent tumor, since no connection between them was demonstrable.

The mucous membrane in the region of the aforementioned papillomas had a variegated appearance. There were areas where the tubules were greatly reduced in number, being replaced by dense infiltrations of round and plasma cells, macrophages and polymorphonuclear leukocytes. In other areas, there were flat and polypoid prominences made up of closely set proliferated glands. Cystic dilatations were in places quite prominent, as were also wide and irregular gastric pits. A number of the epithelial cells covering and lining these pits had undergone goblet cell metaplasia. The muscularis mucosae was thickened and densely infiltrated by inflammatory cells.

COMMENT

The reappearance of symptoms following gastro-entero-anastomosis for peptic ulcer generally indicates a benign complication or sequel. Recurrence of the old or formation of a new ulcer and nonmalignant obstruction are most frequently suspected. Occasionally, however, the clinical manifestations may be produced by a carcinoma. In one such case, that of Schwarz,¹ a patient who had remained well for six years after gastro-enterostomy developed symptoms of obstruction of the stoma, which were due to a malignant growth. In another case, that of Eichelter,³ a neoplasm by encroaching on the lumen of the stoma led to manifestations referable to obstruction of the proximal loop. In a third case, the one herein reported, the carcinoma, being polypoid, produced no clinical obstruction, but gave rise to a set of indistinctive symptoms. The presence of a palpable mass and the roentgen evidence of a filling defect within the gastric silhouette furnished the chief reasons for the preoperative diagnosis of carcinoma of the anastomosis.

The main point of interest centers about a possible causal relationship between the presence of a gastro-enterostomy and the development of a carcinoma. In other words, does a gastro-enterostomy determine in any way the occurrence of a malignant growth, or is the coexistence an accidental one? In the case reported by Schwarz,¹ observations with regard to the tumor were limited to the palpation of a mass at the stoma and the presence of metastases in the adjacent lymph glands and the peritoneum. There was no opportunity for further observation, as excision was not attempted at operation and the patient was still alive when the publication appeared. Whether or not the neoplasm originated in the anastomosis and was actually related to it cannot be ascertained from the facts available. The case of Hurst and Stewart² sheds no light on the problem as no description of the tumor accompanies the report. In Eichelter's³ case, the communication does not include facts that are most pertinent to the question of a causal relationship. The statement that the gastric mucosa at the anastomosis showed thickened folds and tumor formation is suggestive of a hypertrophic gastritis, which may be considered a forerunner of carcinoma (see a later paragraph). Unfortunately for present purposes, the main theme of the paper is the duodenal obstruction, and the gross and microscopic aspects of the new growth are slighted. From the information obtained in Eichelter's

report it would be difficult to establish any relationship between the artificial stoma and the development of the malignant growth. In the case herein described there appears to be adequate evidence to suggest that the occurrence of the carcinoma at the new stoma was determined by the gastro-enterostomy.

There is a growing tendency on the part of pathologists to consider inflammatory hyperplasia, polyposis and carcinoma as merely stages of one pathogenic process. The three types of proliferation are frequently coexistent and accompanied by transitional stages that denote almost unequivocally the development of one from the other. In the stomach, particularly, is the association of inflammatory hyperplasia, adenomatous polyps and polypoid carcinoma a relatively common one. The evidence pointing to a direct relationship between chronic gastritis and carcinoma of the stomach is most convincing. The literature and personal observations indicating the precarcinomatous nature of chronic inflammatory changes in the stomach have been splendidly presented by Konjetzny,⁴ to whose works the reader is referred for more detailed information.

If it is true that chronic gastritis may lead to carcinoma (in a predisposed subject), the malignant growth at the stoma in the case reported here can be reasonably associated with the gastro-enterostomy. The histologic sections demonstrate the presence of chronic inflammatory changes of high grade in the gastric mucous membrane about the anastomosis. Presumably the gastritis was the result of abnormal mechanical and chemical insults due to the altered physiology conditioned by the operation. In addition to the atrophic-hyperplastic changes which constituted part of the gastritis proper there were a number of frankly benign sessile and pediculated polyps. There were also small polypoid growths that contained atypical structures and cells suggestive of "precarcinomatous" proliferation and others that were frankly malignant. Transitions from inflammatory hyperplasia to benign neoplastic overgrowth and from benign to malignant hyperplasia could be readily identified. The presence of several independent carcinomatous polyps also favors the view of an inflammatory etiology, since a multicentric origin is, according to Konjetzny⁴ and others, characteristic of a malignant condition developing from a chronic gastritis. The occurrence of the large polypoid mass just at the stoma is explained by the circumstance that the site of anastomosis was subjected to the maximum injury and was therefore the first to undergo inflammatory and subsequent malignant changes. Whether or not a pyloric carcinoma would have developed had no gastro-enterostomy been performed is open to conjecture.

⁴ Konjetzny, G. E. in Anschutz, W., and Konjetzny, G. E. *Die Geschwulste des Magens*, Deutsche Chirurgie, Stuttgart, F. Enke, 1921, pt. 46, first half, no. 1, p. 26. *Die entstehungsgeschichtlichen Beziehungen der Gastritis zum Karzinom*, in Henke, F. and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1928, vol. 4, pt. 2, p. 904.

THE EFFECT OF PROLONGED DISTENTION OF THE STOMACH IN DOGS

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The mechanism concerned in the production of acute dilatation of the stomach is not fully understood. Numerous theories have been advanced to account for it, but none has been entirely adequate. The reason is perhaps to be explained by the fact that this condition may be brought about in several different ways.

When first described by Brinton¹ it was thought to be primarily a passive phenomenon of a purely paralytic nature. Conner² stated "The absence in almost all cases of obvious obstruction at the pylorus, and the fact that a similar paralytic distention of the intestines is a not uncommon phenomenon after abdominal operations and in peritonitis served to support this view as has also the experimental work of Cannon and Hallion."³ The latter investigators said that "after resection of both nerves (vagi) above the diaphragm we have seen produced in the dog an enormous dilatation of the stomach and of that portion of the esophagus innervated."

The occurrence of acute dilatation of the stomach after section of the vagi, however, is quite rare, since many investigators who have performed this operation in animals have failed to observe it, although they have consistently found a change in gastric peristalsis.⁴ Ivy,⁵ working on dogs, and Patterson⁶ on lower animals, found on making actual measurements that the postural tone of the stomach is decreased after section of the gastric vagi for a period of several days, that is, more

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1 Brinton, quoted by Conner. *Am J M Sc* **133** 345, 1907

2 Conner. *Am J M Sc* **133** 345, 1907

3 Cannon and Hallion, quoted by Conner (footnote 2)

4 Cannon. *Am J Physiol* **29** 250, 1911. Carlson. *ibid* **32** 369, 1913

5 Ivy, A C. *Physiology of Stomach. Studies on Gastric Ulcer*, *Arch Int Med* **25** 6 (Dec) 1920

6 Patterson, T L. *Am J Physiol* **49** 147, 1919, *ibid* **53** 293, 1920

air was necessary to produce a certain intragastric pressure after section of the vagi than before. Loss of vagus tone may be a contributing factor, but not a prime or sole factor.

In the early part of the twentieth century, numerous investigators among them Conner, felt that "the most important single cause of such stomach dilatation is the sudden incarceration of the duodenum between the root of the mesentery which passes in front of it and the vertebral column behind." For a time this condition was widely discussed in this country and elsewhere and became known in the literature as arterio-mesenteric occlusion. More recently, however, numerous investigators have observed acute dilatation to occur within a few minutes or even seconds during the course of an abdominal operation, right under the very eyes of the operator. These occurrences have led to a belief that dilatation may be an active and not a passive phenomenon. This rapid accumulation of gas within the stomach has been due undoubtedly to some process that has shut off the oropharynx from the laryngopharynx and has brought about an expiration of air from the lungs and trachea into the esophagus and stomach. The possibility of this occurrence has been studied recently by McIver⁷ on experimental animals. He came to the conclusion that "the distinguishing feature of acute dilatation occurring under general anesthesia is an active one and not a passive phenomenon. The gas responsible is atmospheric air." Just why this air is diverted into the stomach and not into the nasal passages he does not attempt to say.

However, regardless of the mechanism that may produce dilatation of the stomach the resulting symptoms are quite similar once this condition obtains. The immediate effects are only slight, but if the distention is prolonged over several hours or days the symptoms become very grave, and death will frequently occur unless this condition is promptly relieved.

The cause of death, like the mechanism producing dilatation has never been adequately explained.

The literature contains the reports of numerous cases of patients who have died from prolonged distention of the stomach. There have been numerous theories advanced to explain the cause of death just as there have been to explain the mechanism producing the distention, and the reason for so many theories is probably the same, namely, there are undoubtedly numerous factors that play a rôle in the production of the fatal outcome. In view of the recent work on the cause of death in simple high intestinal obstruction, the rapidly fatal effects of dilatation have been attributed to similar causes, among them the loss of chlorides in the gastric juice the loss of fluids and essential intestinal juices such

⁷ McIver M. A. *Ann Surg* 85 704, 1927

as bile and pancreatic juice coupled with a failure of the organism to obtain nutritive materials and fluids. Undoubtedly these factors play an important rôle in the cause of death. However, the paper of Conner² emphasizes the serious nature of acute dilatation of the stomach and the rapidity with which death ensues unless it is relieved. Further, the pathologic reports included in Conner's paper point out the fact that the stomachs of patients dying of this condition manifest gross and microscopic changes. These changes in the stomach are probably the result of the disturbance of the circulation of the gastric wall and, we feel, may play an important rôle in the fatal outcome. This possibility, we believe, has been overlooked in recent years in view of the emphasis that has been placed on the loss of chlorides in the gastric secretion. But so far as we have been able to find, no one has studied the effects of prolonged distention of the stomach *per se*.

We thought that the effects of distention of the stomach *per se* might be studied by placing a large balloon into the stomach by means of gastrostomy and then distending it with water, a procedure that would prevent the loss of water and chlorides through vomiting and hence avoid this complicating factor. Also, since distention of the stomach may directly or indirectly affect the heart, which condition might be one of the factors concerned in the cause of death from dilatation of the stomach, electrocardiograms were made before and during the period of gastric distention.

EXPERIMENTAL METHODS

We performed gastrostomies on twelve dogs under sterile technic. A large rubber balloon was inserted into the stomach immediately after gastrostomy and was then inflated with varying amounts of water. Enough water was introduced (from 500 to 700 cc) initially to prevent any leakage of gastric juice through the fistula. The balloons were further distended at intervals over periods ranging between twenty-two and seventy-two hours. The total amount introduced varied somewhat with the size of the dog, or varied between 1,200 and 2,250 cc. This amount of fluid was used with the idea in mind that it is about twice the amount of milk that a dog of this size would voluntarily ingest when hungry. Dogs weighing from 15 to 30 pounds were used. Electrocardiograms were made on seven dogs before and at intervals after distention.

RESULTS

The distention of the stomach resulted in the death of all the twelve dogs in from twenty-six to ninety hours. In all the dogs the distention caused retching at the time the fluid was first introduced, but none of the dogs was able to vomit and therefore could not lose fluids and chlorides in this manner. After the first period of retching the animals became more or less adapted to the distention and either did not retch subsequently or only infrequently. Most of them salivated, which

denotes that the nausea-salivary mechanism was probably continuously excited. No fluid was lost via the fistula, except in two instances in which the balloons were ruptured during the night, when this happened a new balloon was introduced and distention again produced. None of the dogs developed diarrhea. An excess of fluid (from 200 to 250 cc) was present at autopsy in the lumen of the intestine in five instances and was present chiefly in the duodenum and stomach.

Blood chlorides were determined in seven of the dogs (dogs 5, 8, 9, 10, 11, 13 and 14), the Van Slyke method being used. Only a very slight fall occurred in six of the seven dogs, the last blood chloride in milligrams per hundred cubic centimeters of blood taken prior to death being dog 5, 430; dog 8, 316; dog 9, 480; dog 10, 430; dog 11, 442; dog 13, 442; and dog 14, 435. The urine was scanty.

Electrocardiograms were made prior to the distention and daily in most cases thereafter on seven dogs. The distention caused a marked acceleration of the heart rate and a disappearance of the sinus arrhythmia which is normally quite marked in dogs. The T wave was negative before distention in six of the seven dogs. Distention caused it to become negative in one dog (no. 5) in which it was positive, and markedly accentuated its negativity in the others. The Q wave was uniformly accentuated. The electrocardiograms of dog 5 are particularly interesting in that there was some evidence of abnormal auricular activity prior to distention as shown by the occurrence of an occasional "ectopic auricular contraction" (?) and a notching or slurring of the P wave. Two and one-quarter hours after distention was induced the suspected ectopic contraction became very evident, being positive in lead 1, diphasic or negative in lead 2 and negative in lead 3. It was regular and of the same voltage as the P wave. Twenty-four hours later the ectopic wave was negative in lead 1. In leads 2 and 3 an occasional ventricular complex was present (fig. 1, 2 and 3). Other occasional irregularities were present in the electrocardiograms which were difficult to interpret.

After the preliminary period of retching, the dogs gradually became more and more depressed, listless and weak and died in coma without muscular twitchings or convulsions.

Autopsy was performed on some dogs immediately after death, and on those dying during the night it was performed early the next morning. There was no evidence of peritonitis in any of the dogs with the exception of dog 6 in which there was some question, and in dog 10 in which a gas bacillus infection was present in the wall of the duodenum. Serosanguineous fluid was present in the peritoneal cavity of nine of the twelve dogs. The stomach was markedly distended in all the dogs as might be expected, as was also the case in dog 14 in which the balloon was found to be ruptured at autopsy. This distention of the stomach

involved the pyloric antrum, which was usually not distended by the balloon. The stomach wall was markedly thinned out and in practically every dog mucosal, submucosal and subserous hemorrhages were present. Hemorrhagic erosions of the stomach were present in some of the dogs. The entire intestine was dilated in three (dogs 2, 5 and 9), the duodenum in two (dogs 3 and 10) and the duodenum and jejunum in one (dog 8). The intestine was either not distended or contracted in six dogs (dogs 1, 4, 6, 11, 13 and 14), the ileum was contracted in one (dog 8) and the ileum and jejunum were normal in one (dog 10). The superior mesenteric vein and the splenic and pancreaticoduodenal veins were always distended, frequently markedly so. The stomach and duodenum were usually markedly congested and discolored. The spleen and pancreas were congested as a rule. Fat necrosis was observed in two dogs. In four dogs the lungs were congested, but otherwise negative.

PROTOCOLS

Only a condensed protocol of each of the twelve experiments will be given. Autopsy records and complete analysis of electrocardiograms will not be included because of lack of space.

Dog 1—Distention of the stomach was produced by introducing 2,000 cc of water over a thirty-four and one-half hour period into a large rubber balloon placed in the stomach by means of gastrostomy. Death ensued within the next twenty-four hours.

Dog 2—Distention was produced as in dog 1, 1,500 cc of water being introduced over a twenty-two hour period. Death ensued in thirty-six and one-half hours.

Dog 3—Distention was produced as before, 2,250 cc of water being introduced over a seventy-two hour period. Lethal issue occurred in approximately ninety hours.

Dog 4—Distention was produced as before, 2,250 cc of water being introduced over a period of sixty-five hours. Death occurred in eighty-five hours.

Dog 5—Distention was produced as in the other experiments. Predistention blood chlorides ranged from 450 to 460 mg per hundred cubic centimeters of blood. The balloon was distended with 1,750 cc of water over a twenty-four hour period. The blood chlorides fell to 430 mg. The dog then pulled the balloon out. Redistention began six days later. The balloon was distended with 2,250 cc of water over a forty-eight hour period. The dog died during the next twelve hour period.

Electrocardiograms taken prior to the first distention showed an inverted T wave in lead 1. On distention, in lead 1 the T wave was inverted, in lead 2 and 3 it was notched and the Q wave was exaggerated. The P wave was distinct, but was occasionally immediately preceded by an irregular ectopic contraction of low voltage. We could not be certain whether this effect was cardiac or somatic. After twenty-four hours of distention, the T wave was positive in all leads with a slight notching at its apex. The heart rate was 280 per minute. The balloon was pulled out by the dog, and six days later an electrocardiogram was made. Lead 1 showed a small diphasic or inverted T wave (fig 1 *AI*). In lead 2, the

T wave was positive (fig 1, *A2*) In lead 3, the P and T waves were notched occasionally, owing to an occasional ectopic contraction of the same voltage as the P wave The balloon was inserted and distended with water Two and one-quarter hours later a rhythmically occurring ectopic contraction was present in lead 1 (fig 2, *B1*) and the T wave was positive In leads 2 and 3 the same abnormality was present, but was negative (fig 2, *B3*) in lead 3 The ectopic contraction had no effect on the ventricle and its rhythm followed the sinus arrhythmia Twenty-four hours later lead 1 showed a negative (fig 3, *C1*) rhythmical ectopic contraction In leads 2 and 3 the ectopic contraction was positive (fig 3, *C2* and *C3*) and an occasional "ventricular complex" (?) occurred

Dog 6—Distention was produced as in the other dogs, 2,000 cc of water being introduced into the balloon within the twenty-two hour period The dog died twenty-six hours after the dilatation was begun

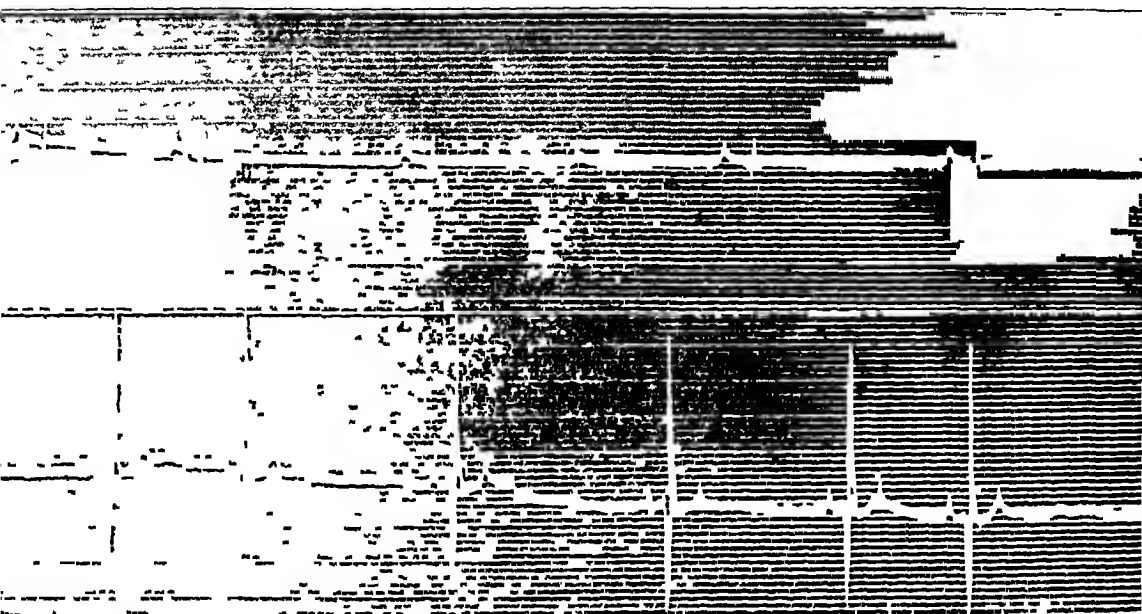


Fig 1 (dog 5)—Control electrocardiograms made prior to the second distention Note in lead 1 (*A1*), the diphasic or inverted T wave and in lead 2 the positive T wave

Dog 8—Distention was produced Electrocardiograms and blood chloride determinations were made before the onset of dilatation of the stomach The blood chlorides ranged from 475 to 490 mg per hundred cubic centimeters of blood Control electrocardiograms (fig 4, *A*) showed a cardiac rate of from 60 to 80 per minute with a marked sinus arrhythmia There was a diphasic or negative or diphasic T wave in all three leads Subsequent studies on other supposedly normal dogs showed this same phenomenon of a negative T wave quite frequently

Distention of the stomach with 2,000 cc of water over a five hour period gave a markedly negative declination of the T and Q waves in leads 2 and 3 (fig 4, *B*) The heart rate was accelerated appreciably and the arrhythmia abolished The dog then pulled the balloon out during the night Redistention was not begun again until three days later, when the blood chlorides were found to be 430 mg Control electrocardiograms at this time showed a rate of 140 with a slight sinus

arrhythmia The T wave was inverted in all three leads (fig 4, C and D) Redistention was begun, 1,500 cc of water was introduced during the afternoon Electrocardiograms taken five hours after the onset showed a marked acceleration of heart rate with abolition of the sinus arrhythmia and a very marked accentuation of the negative T wave (fig 4, E) The balloon was found ruptured the next morning The blood chlorides were the same Electrocardiograms revealed a rate of 90 per minute with a reappearance of the sinus arrhythmia The T wave was broadened and was again dichrotic The increase in voltage was to be noted and the appearance of a Q wave in lead 1 The balloon was redistended during the morning and afternoon with 1,750 cc of water The blood chlorides were 320 mg at 5 p m Electrocardiograms taken the following day at 2 p m, i e, twenty-eight hours after distention, with 2,250 cc of water in the balloon, revealed a marked tachycardia with a moderately accentuated negative T wave in all leads

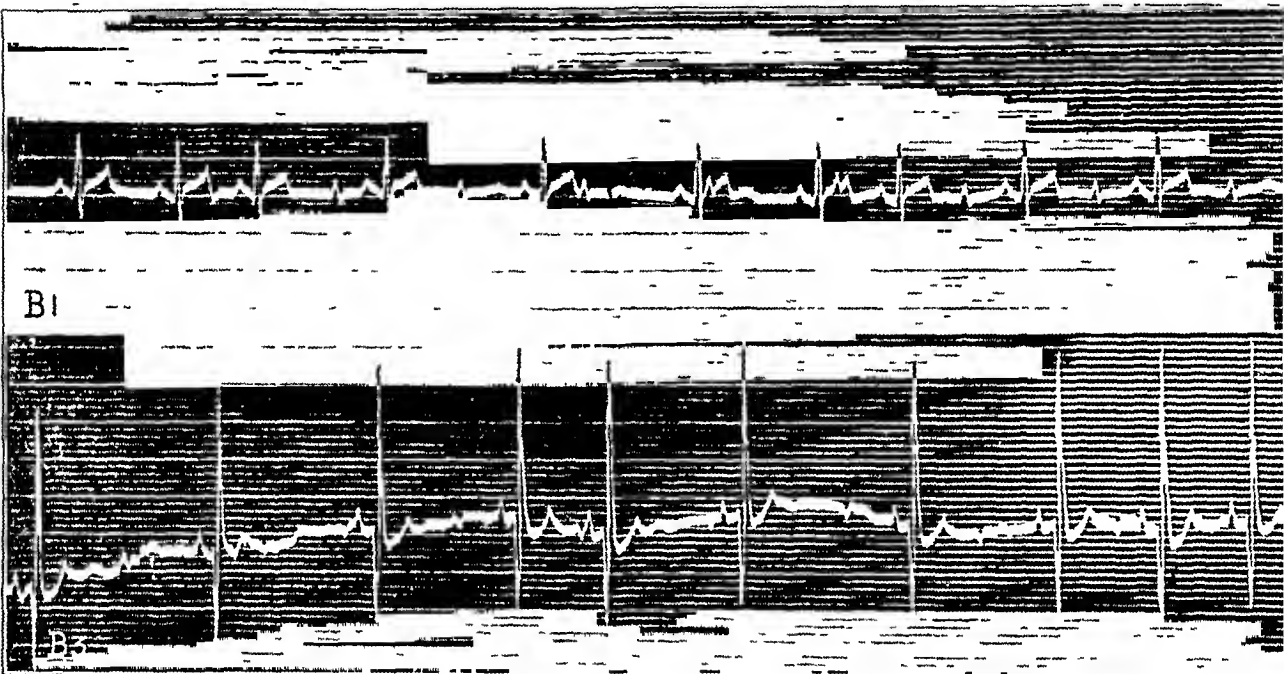


Fig 2 (dog 5)—Electrocardiograms made two and one-quarter hours after distention of the stomach Note that the T wave is positive and that there is a rhythmically occurring ectopic contraction Measurements show that it is influenced by the sinus arrhythmia The ectopic contraction is negative in lead 3 (B3)

(fig 4, F) An occasional complex occurred which was difficult to interpret The blood chlorides at this time were 316 mg The dog was alive at 11 p m thirty-seven hours after the onset of the third distention, but died some time before 8 a m

DOG 9—Distention was produced as in the other dogs Predistention blood chlorides were 520 mg The electrocardiogram was normal except for sinus arrhythmia and an inversion of the T wave Distention was begun at 12 noon, 1,200 cc of water was introduced by 4 p m The blood chlorides at 4 30 p m were 480 mg, electrocardiograms showed a disappearance of the arrhythmia and a marked acceleration in rate The dog was found dead at 8 a m the next morning

DOG 10—Distention was produced as before Predistention blood chlorides ranged between 470 and 474 mg per hundred cubic centimeters of blood Electro-

cardiograms showed a rate of 110 and a QRS complex of low amplitude. The T wave was inverted in leads 2 and 3 and flattened in lead 1. Distention was produced with 1,000 cc of water all at one time, i. e., approximately twenty minutes were required to introduce it. When between 700 and 800 cc had been inserted, the dog retched some. Twenty-four hours later 500 cc more was introduced. Respiratory distress, frothing at the mouth and retching were noted. Electrocardiograms taken nineteen hours after distention showed more marked inversion of the T wave, abolition of the arrhythmia and a rather marked tachycardia. The blood chlorides twenty-four hours after the dilatation were 430 mg per hundred cubic centimeters. The dog died within thirty-six hours of the onset of the experiment.

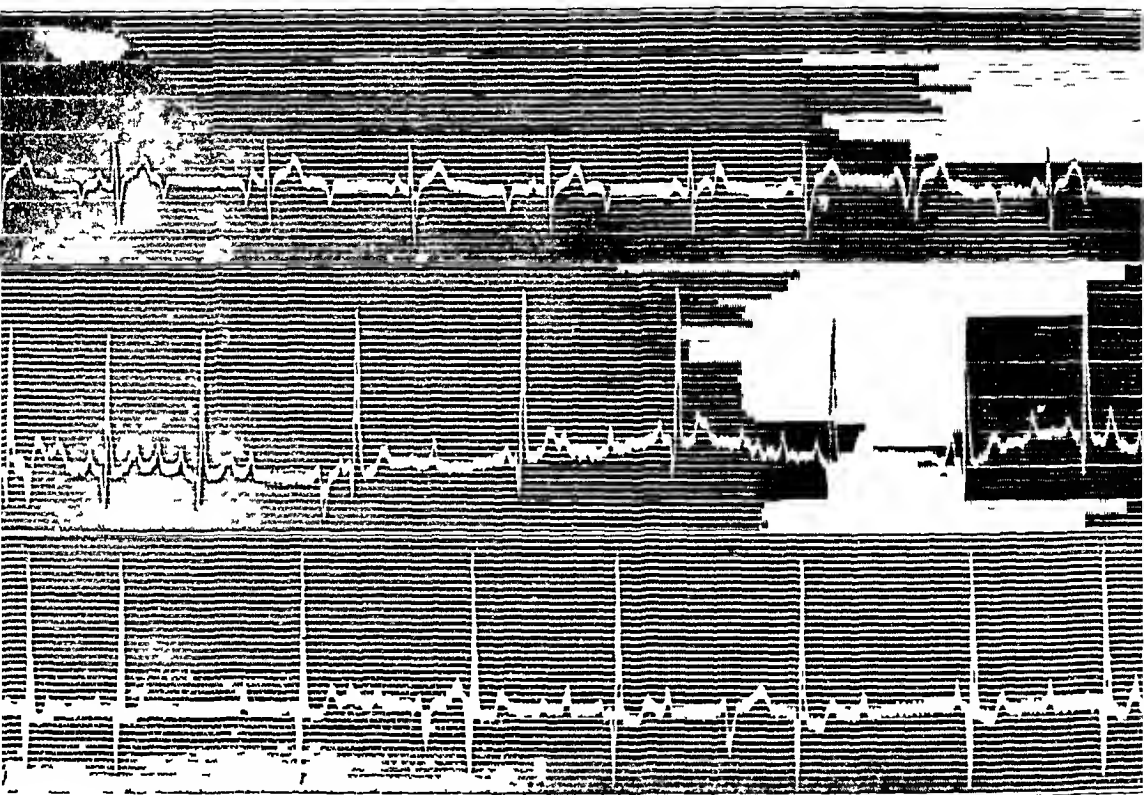


Fig 3 (dog 5)—Electrocardiograms made twenty-four hours after continuous distention. Note the negative ectopic rhythmical contraction in lead 1 (C1) and that it is positive in lead 2 (C2) and lead 3 (C3). Lead 3 (C3) shows a "ventricular complex" that occurred occasionally.

Doc 11—Distention was produced as in the other experiments. The dog was all brown with long hair. Predistention blood chlorides were 480 mg. Electrocardiograms showed a rate of 120 and a slight sinus arrhythmia. The T wave was inverted in all three leads (fig 5, A). Distention was produced with 1,000 cc of water. Retching occurred when 700 cc had been added. Five hundred cubic centimeters was added first, then 500 cc thirty minutes later. Electrocardiograms taken nineteen hours later showed a marked accentuation of the negative T wave, abolition of the arrhythmia and a marked acceleration of the cardiac rate (fig 5, B). The blood chlorides twenty-four hours after distention were 442 mg. Five hundred cubic centimeters more of water was added. The dog died within thirty-six hours.

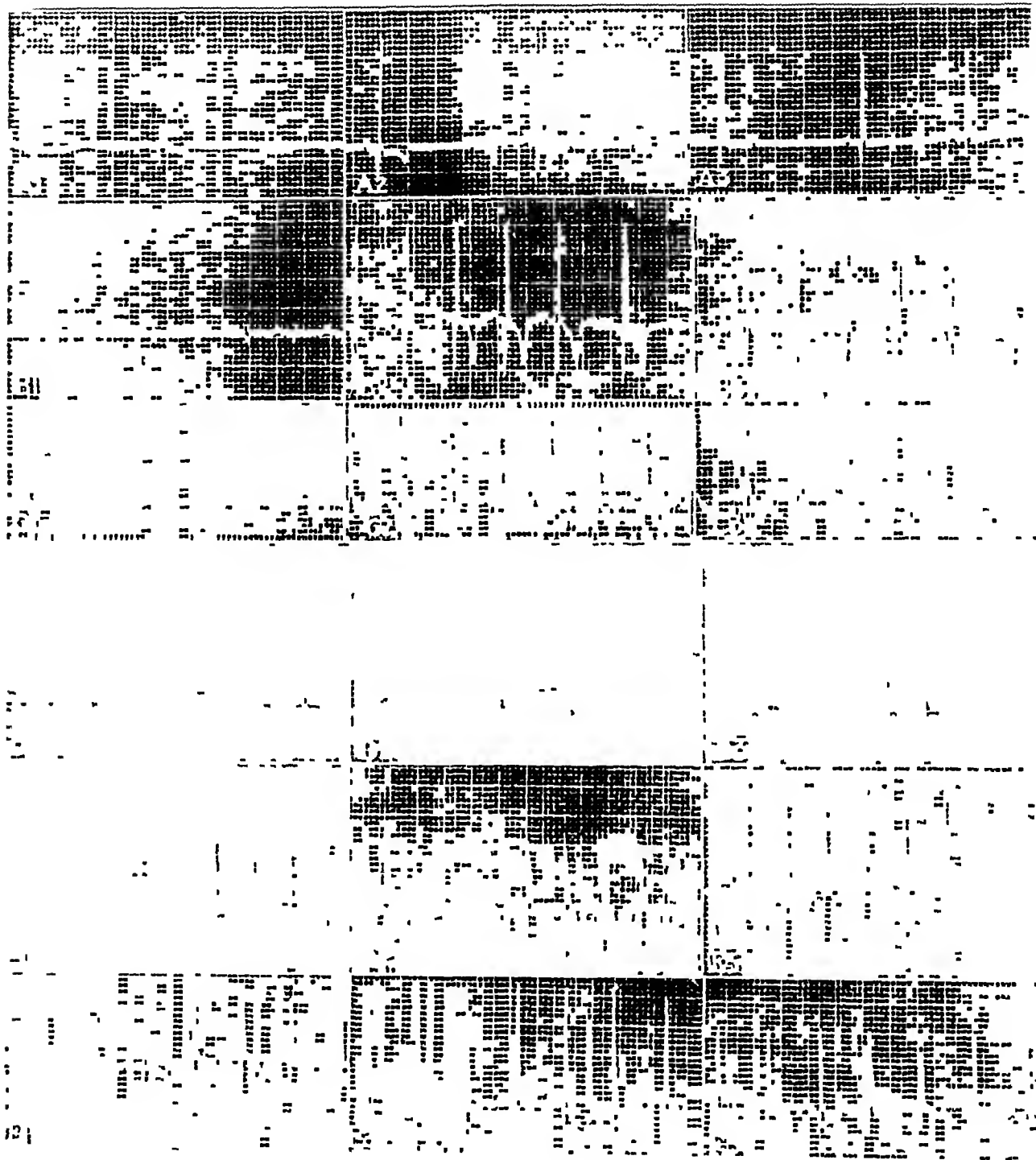


Fig 4 (dog 6) —The A series is the control electrocardiogram. The B series was taken immediately after distention. Note the tachycardia and accentuation of the T wave. The balloon was pulled out. The C series was taken twenty-eight hours after the second distention, when the dog was quite sick. The balloon was pulled during the night. Series D was taken the following afternoon. Note the increase in voltage in lead 1 and that the tachycardia has persisted for from twelve to eighteen hours after release of distention. The stomach was distended again. Series E was taken five hours after the third distention. The balloon ruptured the next morning. An electrocardiogram was taken. Then the stomach was distended again and twenty-eight hours later series F was taken. The dog died at thirty-seven hours.

DOG 13—Distention was produced as in the other experiments. The dog was a white fox terrier. Predistention blood chlorides were 460 mg per hundred cubic centimeters of blood. Electrocardiograms showed a rate of 90 with a negative T wave in all three leads (fig 6, *A*) and a moderate sinus arrhythmia. One thousand cubic centimeters of water was introduced over a ten minute period. Nausea and retching were noted when 700 cc had been introduced. Electrocardiograms taken nineteen hours after distention showed a rate of 240 per minute

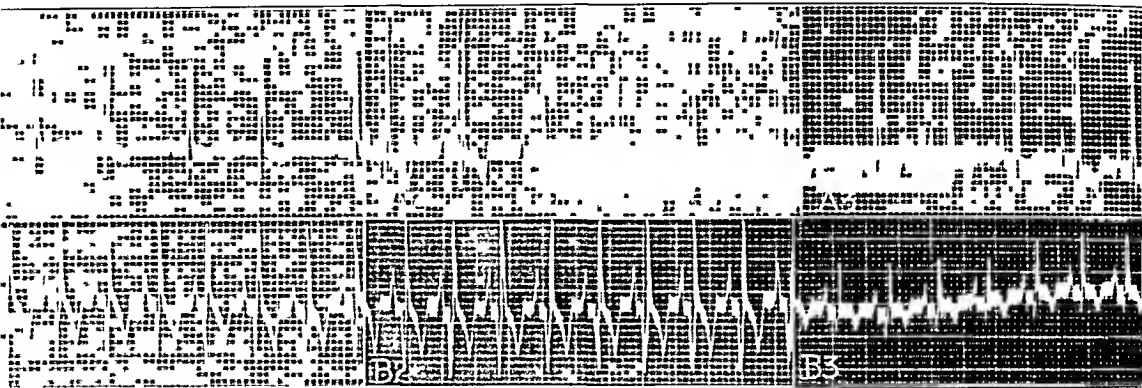


Fig 5 (dog 11)—Series A is the control electrocardiogram. Series B was taken nineteen hours after distention.

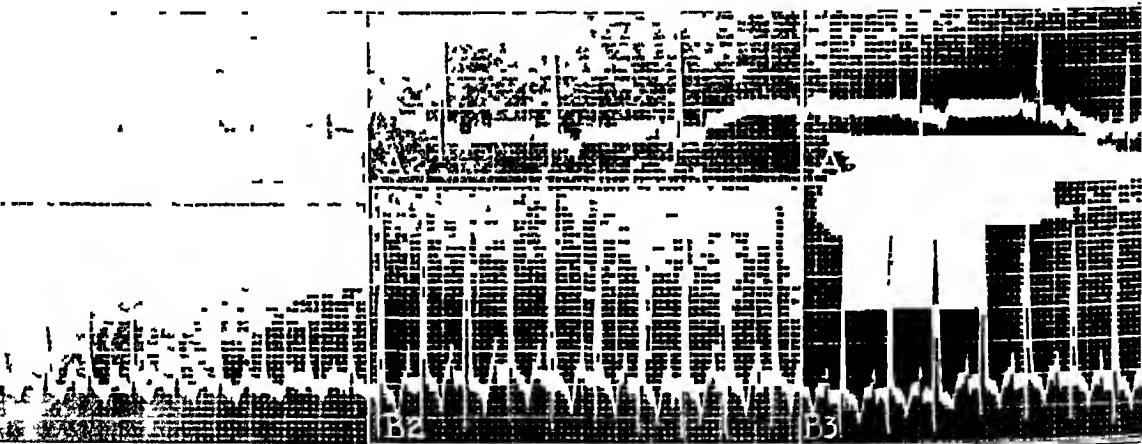


Fig 6 (dog 13)—Series A is the control electrocardiogram. Series B was taken nineteen hours after distention.

with an abolition of the sinus arrhythmia. The T wave was negative in all three leads and moderately accentuated (fig 6, *B*). The blood chlorides twenty-four hours after distention were 442 mg per 100 cc of blood. Five hundred cubic centimeters more of water was added. After the addition of 300 cc, dyspnea, frothing at the mouth and retching were noted. The dog died during the night, less than thirty-six hours after the onset of the distention.

DOG 14—The dog was all brown, with long hair and a long tail. Predistention blood chlorides ranged between 476 and 509 mg per hundred cubic centimeters. Electrocardiograms showed a rate of 100, a slight sinus arrhythmia, an inversion

of the P wave in lead 3 and an inversion of the T wave in leads 2 and 3. The negative T waves were rather marked. In lead 1 the T wave was positive. Distention was produced with 1,000 cc of water over a fifteen minute period. Fifteen minutes later the dog vomited a small amount of frothy material. The balloon was found to be ruptured the next morning. Blood drawn for the chloride determination showed 457 mg per hundred cubic centimeters. The balloon was reinserted and distended with 750 cc of water. Slight respiratory distress and retching occurred during distention. Electrocardiograms taken immediately afterward showed a positive P wave in lead 3. There was a moderate tachycardia, and the sinus arrhythmia was abolished. Blood chlorides twenty-four hours after redistention were 433 mg. Electrocardiograms twenty-six hours after a second distention were quite similar to the previous electrocardiograms. The negative T wave was slightly more accentuated and the rate more rapid (180). The blood chlorides at thirty-one hours were 420 mg, at forty-eight hours, 435 mg. Electrocardiograms at forty-nine hours showed a similar picture except that the negative T wave was not so marked. Two hundred cubic centimeters more of water was added at fifty hours. The dog died during the night, after living approximately sixty-five hours.

COMMENT

These results show that distention of the stomach *per se* may lead to changes that are sufficient to cause death in from twenty-six to seventy-two hours. The experiments being of such a nature that loss of chlorides and dehydration could not result from vomiting, these two factors may be ruled out as important in the cause of death in our experiments, and indicate that they are only contributory factors in the cause of death in acute dilatation of the stomach as it occurs clinically.

The changes at autopsy in these animals although more severe coincide for the most part with the pathologic changes in cases of acute dilatation of the stomach in man as reported by Conner.² The anatomic changes are those that one might predict to occur on the basis of an arteriomesenteric occlusion and of a blockage of the venous return by the increased intragastric pressure. These factors have been elucidated by the experimental work of Dragstedt and Dragstedt,⁸ Van Zwalenburg,⁹ Gatch, Trusler and Ayers,¹⁰ and Dragstedt, Lang and Millet.¹¹

Although we believe from the clinical picture that dogs with a distended stomach present some element of shock, we feel more certain that the chief cause of death is a toxemia that results from

⁸ Dragstedt, C. A., and Dragstedt, L. R. Acute Dilatation of the Stomach, *J. A. M. A.* **79** 612 (Aug. 19) 1922.

⁹ Van Zwalenburg. *Ann. Surg.* **46** 780, 1907.

¹⁰ Gatch, W. D., Trusler, H. M., and Ayers, K. D. Effects of Gaseous Distention on Obstructed Bowel. Incarceration of Intestine by Gas Traps, *Arch. Surg.* **14** 1215 (June) 1927.

¹¹ Dragstedt, L. R., Lang, V. F., and Millet, R. F. Relative Effects of Distention on Different Portions of the Intestines. *Arch. Surg.* **18** 2257 (June) 1929.

the absorption of toxic products from cellular trauma or destruction due to the disturbed circulation. This is shown by an experiment (Drs Ivy and Burgess) in a dog in which pyloric obstruction was produced after section of both vagi and splanchnic nerves. Vomiting and death occurred but were delayed only about one day when compared to controls. Dragstedt and Dragstedt⁸ stated that the symptoms of acute dilatation of the stomach, which often makes it difficult to distinguish this condition from intestinal obstruction, "are those of a severe toxemia rather than the result of reflex or mechanical effects from the stretched and dilated stomach." We agree with this statement and believe that the toxemia is due indirectly to the distention which produces such an obstruction to venous return that tissue damage and a disturbance of the normal phenomena of selective absorption result. The interference with venous return obviously embarrasses the circulatory mechanism, as is shown by the marked acceleration of the heart. In addition, the encroachment of the distended stomach on the adjacent organs and tissues causes a partial obstruction to their blood supply. That there may be an altered permeability of the mucosa to products in the lumen of the stomach and duodenum and that there may be toxic products entering the circulation from this source or even the peritoneal cavity is very likely, as has been maintained by Hartwell¹² and Brooks¹³ and their co-workers. That bacteria may invade the injured gastric wall and play a rôle in the production of toxins is evidenced by the fact that immediately post mortem one of our dogs grossly manifested gas bacillus invasion of the wall of the duodenum. The fact is that prolonged distention of the stomach produces grave morbid changes in the stomach wall which are evident to the unaided eye and which are analogous to the changes reported by numerous workers that occur in the intestine in intestinal obstruction.

A review of our protocols shows that the distention must be present for a considerable period of time before irreversible changes occur which is well known clinically. If the balloons ruptured or if the distention was released within eighteen to twenty-four hours, the animals survived. Our observations on this point are only suggestive, and because of the variability in the length of life, a large series of animals would have to be used in order to make an accurate statement.

It should be pointed out that in some of our dogs the picture was that of strangulation, in others that of duodenal obstruction with strangulation. Further, it should be kept in mind that with the stomach

12 Hartwell, J. A., Houget, J. P., and Beckman, F. An Experimental Study of Intestinal Obstruction, *Arch. Int. Med.* **13** 701 (May) 1914, *Am. J. M. Sc.* **143** 357, 1912, *J. Exper. Med.* **18** 139, 1913.

13 Brooks, B., Schumacher, H. W., and Wattenburg, J. E. *Ann. Surg.* **67** 210, 1918. Copher, G. H., and Brooks, B. *Ann. Surg.* **78** 755, 1923.

markedly distended by the method employed in our experiments, some esophageal obstruction is probably present, and hence, the factors operating in the cause of death in esophageal obstruction may have played some rôle in the cause of death in our dogs.

We were caused to study the heart closely in these experiments because of the well known clinical relation of gastric distention and digestive disturbances to angina pectoris, coronary thrombosis, tachycardia and cardiac irregularities. In the clinical texts it is generally stated that acute dilatation of the stomach causes a tachycardia, but that it is slow in onset and related to the toxemia. Vaquez,¹⁴ in discussing tachycardia, stated that distention of the stomach by aerophagia is an occasional cause of this condition. MacKenzie¹⁵ stated that distention of the stomach or colon with gas may lead to cardiac embarrassment. It is well known that tapping the stomach or viscera in the frog causes a slowing of the heart rate. But we have been unable to find any reports on the effect of experimental distention of the stomach on the heart except that of Carlson and Luckhardt¹⁶ in turtles in which distention of the stomach usually caused acceleration. Our results show that immediately following the distention of the stomach a tachycardia results, except during retching when there occurs the well known vagus slowing and irregularity of cardiac rate. This immediate or early increase in cardiac rate must be due either to reflexes or to a disturbance of the diastolic filling of the heart, or both. We have not sectioned the nerves to ascertain the true mechanism, but in the turtle it does not result after section of the cardiac vagi.¹⁶ After the onset of the toxemia the tachycardia is probably due in part to the effect of toxins. The abolition of the normal sinus arrhythmia is related or due to the tachycardia. The inversion of the T wave and the accentuation of the negative T wave is best explained, we believe, as due to a change in the anatomic axis¹⁷ caused by the distention of the stomach. We explain the accentuation of the Q wave in the same manner. The decrease in the accentuation of the T wave when the dogs were markedly toxic, we interpret as due to a failing heart.¹⁷ The marked changes that occurred in the electrocardiograms of dog 5 (figs 1, 2 and 3), which manifested possible evidence of abnormal activity of the auricles prior to gastric distention, show that given an abnormal heart to begin with, gastric distention may augment the disturbance. However, since

14 Vaquez, Henri. *Diseases of the Heart*, trans. by Henry Laidlaw, Philadelphia, W. B. Saunders Company, 1924.

15 Mackenzie, James. *Diseases of the Heart*, London, Oxford University Press, 1921, p. 360.

16 Carlson, A. J. and Luckhardt, A. B. *Am J Physiol* **55**: 31, 1921.

17 Katz, L. N. *Physiol Rev* **8**: 447, 1928.

we are not certain that the heart of this dog manifested a slight abnormality prior to distention, it is possible that the distention of the stomach was solely responsible for the postdistention abnormalities

SUMMARY

1 Continuous distention of the stomach with a volume of water introduced into a balloon—a volume twice that which would be ingested in the form of milk in hunger—caused grave morbid changes to occur in the wall of the stomach and resulted in death in twelve dogs within a period of from twenty-six to ninety hours without a significant fall in blood chlorides and dehydration. The cause of death was toxemia, the mechanism of the production of which is discussed. The changes found at autopsy were not unlike those reported to occur in man in acute dilatation of the stomach.

2 An electrocardiographic study revealed that distention of the stomach causes (*a*) a tachycardia with abolition of the normal sinus arrhythmia manifested by dogs, (*b*) inversion of the T wave or the accentuation of an inverted T wave present in some normal dogs, (*c*) accentuation of the Q wave and (*d*) an exaggeration of preexisting electrocardiographic abnormalities.

NORMAL, ABSENT AND PATHOLOGIC TONSILS IN YOUNG WOMEN

A COMPARISON OF PHYSICAL MEASUREMENTS *

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In an attempt to evaluate the arguments for the removal of tonsils, a study of the histories and physical measurements of young women entering the University of California from 1920 to 1929 was undertaken. The nature of the physical examination required at entrance, the selection of cases studied, the statistical method of handling the data and the comparisons of the histories of those with normal tonsils of those whose tonsils had been removed and of those with pathologic tonsils have been reported ¹

The comparison of the physical measurements and of the menstrual experiences of the three groups is here attempted, and should probably carry more conviction than a comparison of histories, since the histories are based on subjective evidence, and are faulty through defective interpretation and memory, while physical measurements are largely objective and faulty only at the hands of the examiner and recorder.

The measurements available for comparison are height, deviation of weight from an arbitrarily selected standard for age and height, capacity of the chest, posture, character and number of abnormal vertebral curves, the arches of the feet, complexion, presence and distribution of acne, presence of enlarged cervical glands, character of the thyroid gland, cardiac conditions, heart rate and systolic blood pressure and the condition of the eyes, ears, nasal cavities and teeth. Menstrual experiences are contrasted in age of onset, length of duration of flow, amount of flow, amount of pain and the presence or absence of irregularity. All measurements are not available for all items for the full ten year period. Capacity of the chest and posture, for instance, were recorded for only the last half of the ten year period.

The statistical material here presented is reliable for comparative purposes when such factors as the accuracy and judgment of the examiner, the excitement of the patient and the methods of measurement

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1 Cunningham, R L. Normal, Absent and Pathologic Tonsils in Young Women. A Comparison of Histories. Arch Int Med 47:513 (April) 1931

similarly affect the three groups contrasted. The records should not form the basis from which standards of physical measurements for young women are derived unless full allowance is made for the nature and method of the examination.

EXPERIMENTAL DATA

Height, Weight and Capacity of the Chest—Heights were taken without shoes and recorded in inches and tenths of inches. The mean heights of those with normal tonsils, 63.45 inches, and of those whose tonsils had been removed, 63.64 inches, give a difference of percentages of 0.19 inches, which is greater than three times the standard error of the difference of the means or the amount that can be attributed to chance and is therefore statistically significant (table 1). The mean height of those with pathologic tonsils was 63.55 inches, which was midway between the mean heights of the other two groups, and not significantly different from either of them.

The greater stature of those whose tonsils had been removed may find explanation in favorable health changes that follow the removal of tonsils. It is, however, possible that concealed factors, such as heredity, past health or standards of living, may be effective in the selection of these groups and may express themselves in certain physical measurements. For instance, tonsillectomy is not as frequent an operation in many foreign countries as it is in the United States. It would therefore be improbable that children of foreign birth or parentage should as frequently have tonsils removed as children of American ancestry. Higher percentages of children who are often ill than of children who are less often ill have tonsils removed.¹ The economic status of the family at times determines whether children shall keep or part with their enlarged tonsils. Other factors than the three mentioned may be present though not apparent, in the groups of persons selected on the basis of their tonsillar condition and may affect height as well as other physical measurements.

The largest number of weights were taken in light gymnasium suits. During the last three years, students were weighed in bathing suits. A relatively small number were weighed in ordinary clothes without coats, sweaters or shoes. Since judgments as to the state of nutrition are based on a coordination of age, weight and height, it was necessary to select an age, weight and height standard in order to obtain deviations from normal or average weight. When this study was undertaken, the actuarial table of the insurance companies² seemed most acceptable and

² Medico-Actuarial Mortality Investigation, compiled and published by the Association of Life Insurance Medical Directors and the Actuarial Society of America 1912, vol. 1.

TABLE 1—*The Means of a Series of Measurements of Physical Characteristics of Young Women with Various Types of Tonsillar Conditions, and the Differences Between These Means and the Measure of the Statistical Reliability of the Differences, That Is, Three Times Then Standard Errors**

Physical Characteristic	Means of Physical Characteristics						Differences of the Means				Three Times Standard Error of the Difference of the Means				Tonsil Group Having the Significant Health Advantage
	Tonsils Normal		Tonsils Absent		Tonsils Pathologic		Normal Absent		Normal Pathologic		Normal Absent		Normal Pathologic		
	Mean	Standard Deviations	Mean	Standard Deviations	Mean	Standard Deviations	Normal Absent	Normal Pathologic	Normal Absent	Normal Pathologic	Normal Absent	Normal Pathologic	Normal Absent	Normal Pathologic	
Mean number of damaged teeth †	9.55	4.9	9.49	4.8	9.35	4.5	0.06	6.20	0.14	0.37	0.41	0.42	63.53		
Mean height, inches	63.46	1.4	63.64	1.4	63.55	1.4	0.18†	0.09	0.09	0.09	0.10	0.11	Absent		
Mean weight deviation, pounds	-3.27	14.3	-2.43	15.5	-1.21	15.8	0.84	2.06†	1.22†	1.00	1.13	1.16	Pathologic and absent		
Mean chest capacity, liters	2.98	0.5	3.01	0.5	3.03	0.5	0.03	0.03†	0.02	0.04	0.02	0.02	Pathologic		
Mean systolic blood pressure	116.06	11.7	115.67	12.2	116.62	12.2	0.39	0.56	0.93†	0.79	0.87	0.61	?		
Mean pulso rate	89.76	13.6	88.82	14.2	89.71	14.3	0.94†	0.07	0.89	0.91	0.99	1.02	Absent		
Mean climacteric period, years	13.28	1.27	13.17	1.25	13.29	1.28	0.11†	0.01	0.12†	0.08	0.09	0.09	?		
Mean duration of menses, days	4.81	1.16	4.88	1.15	4.81	1.14	0.07	0.00	0.07	0.07	0.08	0.08			

* The original figures from which the percentages, means and standard deviations have been calculated are on file and available for consultation. This study includes 1,185 women with normal tonsils, 4,134 women whose tonsils had been removed, and 2,886 women with pathologic tonsils.

† In students with no teeth absent

‡ Statistically significant difference

was selected for this purpose. The weights on which actuarial tables are based were taken without shoes, but in light clothes, and must, therefore, be a few pounds heavier than weights taken for this study.

Those with normal tonsils were most underweight (table 1), those with pathologic tonsils least underweight. The differences in means of weight deviations of the groups with normal tonsils and pathologic tonsils and of the groups without tonsils and with pathologic tonsils are statistically significant. If these nutritional variations are credited to the condition of the tonsils, there is no argument in this field for the removal of pathologic tonsils. Concealed factors may, however, be effective here, as well as in mean height determinations.

For the determination of the capacity of the chest, the spirometer was used and the greatest amount of air expired, measured in liters. Since the use of the spirometer was new to many subjects, they were often given two or more trials, and the highest figure registered was accepted for record (table 1). There was a significant difference between the mean capacity of the chest of those with normal and of those with pathologic tonsils. The latter group had the greater mean capacity (table 1).

Posture, Vertebral Curves and Feet—Estimates of posture in terms of *A, B, C, D* and *E* were recorded for all entering students who were required to register in physical education classes³ (table 2). The numbers in the superior, *A*, rating, and in the poorest, or *E*, rating, were so small as to be almost negligible. The groups of those whose tonsils had been removed and of those with pathologic tonsils had practically the same incidence in the *B, C* and *D* ratings. The significance of the higher percentages of those with normal tonsils in the *C* rating was minimized or nullified by the lower percentage of persons of this group in both the better, or *B*, rating, and the less favorable, or *D*, rating. There seems, therefore, to be no appreciable influence of tonsillar condition on posture.

Where vertebral curves assumed unusual degrees, they were recorded as instances of kyphosis, lordosis and scoliosis (table 2). For 9,951 students for whom such criticisms of the vertebral column were made, the incidence in the three groups differed by less than 2 per cent. Such differences in percentages are too small to have statistical significance. Tonsillar condition does not seem to relate itself to any type of exaggerated vertebral curvature.

The character of the arches of the feet was carefully observed and recorded, although not in the same terms, for the ten year period. For a number of years, the designations of high, medium and flat were used.

³ Klein, Armin. Posture Clinics, United States Dept. Labor, Children's Bureau, 1926, p. 164.

TABLE 2—The Percentages of Incidence of Physical Characteristics in Young Women with Various Tonsillar Conditions, with Differences Between These Percentages and the Measure of the Statistical Reliability of the Differences, That Is, Three Times Then Standard Errors

Physical Characteristics	Percentage Incidence of Physical Characteristics				Difference in the Percentage Incidences				Three Times Standard Error of the Difference of Percentages				Tonsil Group Having the Significant Health Advantage
	Tonsils Normal		Tonsils Absent		Normal Absent		Pathologic Absent		Normal Absent		Pathologic Absent		
	Tonsils Normal	Tonsils Absent	Tonsils Normal	Tonsils Absent	Normal Absent	Pathologic Absent	Normal Absent	Pathologic Absent	Normal Absent	Pathologic Absent	Normal Absent	Pathologic Absent	
Blond skin	19.09	17.73	20.59		1.36	1.50	2.86	2.58	2.94	2.91			
Demiblonde skin	48.14	50.44	48.55		2.00	0.12	1.88	3.33	2.69	3.68			
Brunette skin	12.46	31.83	30.85		0.61	1.61	0.93	3.12	3.42	3.42			
Aene of face	11.23	8.80	10.60		2.43*	0.63	1.80	2.01	2.31	2.20			Absent
Aene of chest	13.60	10.30	11.61		3.20*	1.90	1.31	2.16	2.43	2.30			Absent
Aene of back	20.83	16.31	13.50		4.53*	2.31	2.19	2.59	2.71	2.81			Absent
Cervical glands enlarged	21.61	22.85	20.79		1.24	0.82	2.06	2.76	3.00	3.04			Normal and absent
Thyroid normal	74.33	74.70	71.15		0.37	3.15*	3.53*	2.88	2.97	2.93			Normal
Thyroid adolescent	23.40	21.82	25.82		1.53	2.42	4.00*	2.76	3.15	3.14			Normal
Thyroid with adenoma	2.26	3.41	2.94		1.15*	0.63	0.47	1.08	3.72	1.27			Normal
Posture A	1.40	1.27	1.31		0.13	0.69	0.04	0.90	1.59	1.57			Normal
Posture B	23.99	28.46	27.61		4.47*	3.62	0.85	3.36	6.21	6.22			Normal
Posture C	62.43	53.58	55.75		8.85*	6.68	2.17	3.75	6.96	6.91			Normal
Posture D	11.53	16.09	14.63		1.56*	3.10	1.46	2.58	4.89	4.93			Normal
Posture E	0.63	0.80	0.70		0.06	0.05	0.11	0.60	1.17	0.54			
Vertebral kyphosis	15.05	15.89	16.68		0.81	1.63	0.79	2.67	5.87	5.83			
Vertebral lordosis	8.73	9.91	9.36		1.21	0.63	0.58	2.13	4.56	4.57			
Vertebral scoliosis	20.76	18.37	19.90		2.39	0.56	1.53	2.94	6.30	6.23			Absent
Long arch of foot high	14.55	19.38	16.73		1.83*	2.18	2.65	2.58	2.79	2.93			
Long arch of foot medium	75.70	75.78	77.78		0.48	2.48	2.00	2.94	3.21	3.23			
Long arch of foot low or flat	10.14	4.83	5.72		5.31*	4.62*	0.69	1.79	1.98	1.70			Absent and pathologic
Anterior arch of foot present	77.92	75.27	75.07		2.65	2.85	0.20	2.91	3.21	3.31			
Height of both eyes 20/20	56.46	55.52	59.71		0.94	3.25	1.19*	3.36	3.69	3.60			Pathologic
Eyes farsighted	23.95	21.72	21.07		0.77	2.88	3.65*	2.91	3.12	3.02			Pathologic
Eyes nearsighted	19.26	19.99	19.38		0.73	0.12	0.61	2.67	2.94	2.99			
Eyes astigmatic	20.72	17.57	14.91		3.15*	5.81*	2.66	2.64	2.82	2.76			Pathologic and absent
Ears normal	93.86	93.39	91.80		0.03	1.56	1.59	1.63	1.92	1.94			
Nose normal	71.68	70.11	61.81		1.27*	12.84*	8.57*	2.94	3.99	3.47			Normal and absent
Nasal spur present	7.35	7.36	9.15		0.01	1.80	1.79	1.71	2.01	2.03			
Nasal septum deviated	16.87	20.12	27.02		10.15*	10.15*	6.90*	2.55	1.03	1.13			Normal and absent
Chronic rhinitis	2.78	3.01	4.11		0.26	1.33	1.07	1.11	1.31	1.17			
All teeth present	71.30	73.55	70.81		2.25	0.46	2.71	2.91	3.30	3.28			
No teeth absent and no fillings	3.95	3.22	4.58		0.73	0.63	1.36	1.50	1.71	1.75			

* Statistically significant difference

Recently, the four grades of high, medium, low and flat have been recorded. For purposes of simplicity the three groups, high, medium and low, which includes flat, have been interpreted from other designations and thus recorded (table 2).

It would seem that normal tonsils and poor feet go hand in hand, since the group of those with normal tonsils had fewer high arches and considerably more low and flat longitudinal arches than either of the other two groups. The anterior arches were present in from 75 per cent to 78 per cent of subjects in all of the groups, and differences in percentages between any two are without significance.

The longitudinal arches of the feet and the condition of the tonsils are interdependent or dependent on some common factor. The largest number of persons with poor feet were found among those with normal tonsils.

Skin, Thyroid and Lymph Glands—Since both the skin and the superficial layers of tonsillar tissue are of the same embryologic origin, it seems possible that a characteristic or pathologic condition of the former might be reflected in the latter. Blonds, demiblonde, demibrunettes and brunettes included approximately the same percentages of persons with normal tonsils, tonsils that had been removed and pathologic tonsils. Apparently, complexion does not predispose to pathologic change or normality of the tonsils. Acne offers more affirmative evidence of a relation to tonsillar condition than does complexion. Those whose tonsils had been removed had clearer faces, chests and backs than did either of the other two groups (table 2). If it were not for the fact that those with pathologic tonsils had clearer skins than those with normal tonsils, and almost as clear skins as those whose tonsils had been removed, there would be an argument for the removal of tonsils, especially in cases in which acne is persistent or disfiguring.

The condition of the tonsils had little effect on the presence or absence of palpable cervical glands, since differences in the percentages of their occurrence in the three groups were within the limits of error due to chance selection (table 2).

A definite relationship seems to exist between the condition of the tonsils and that of the thyroid gland. About the same percentages of those with normal tonsils and of those whose tonsils had been removed had a normal thyroid gland, while fewer of those with pathologic tonsils had a normal gland (table 2). Those with pathologic tonsils had a significantly higher number of adolescent enlargements of the thyroid than those with normal tonsils or those whose tonsils had been removed, while those without tonsils had the highest percentage of adenomas of the thyroid of the three groups.

Cardiac Conditions and Blood Pressure—Evidence of cardiac disease as determined by physical examinations was discussed in the article already presented,¹ since such evidence is related so intimately to the history of cardiac disease and rheumatism. Although there were some suggestive relationships between the tonsillar condition and pathologic change in the heart, none were sufficiently clear to warrant definite conclusions.

The curves of the pulse rates of those with normal tonsils, of those without tonsils and of those with pathologic tonsils were very similar. The mean pulse rate of those whose tonsils had been removed was significantly, though slightly, less than the means of either those with normal tonsils or those with pathologic tonsils (table 1). Since all of the mean pulse rates in this study were considerably above the accepted average, or normal, the group of those whose tonsils had been removed most nearly approached normal.

The mean blood pressure of the group of those whose tonsils had been removed was lower than the mean of either of the other two groups (table 1), the difference between the means of those with normal tonsils and of those without tonsils was small enough to credit to the chances of simple sorting, while the difference between the means of the blood pressures of those without tonsils and of those with pathologic tonsils was great enough to deserve an explanation. As yet, there is no accepted optimum of blood pressure for various age groups, so it is difficult to decide whether those with no tonsils and a mean blood pressure of 115.67 mm of mercury or those with pathologic tonsils and a mean blood pressure of 116.62 mm are most fortunate.

The effect of the condition of the tonsils on the heart and the circulation was slight, and was difficult to evaluate and to interpret.

Eyes, Ears and Nose—The eyes of students entering the University of California were examined by an oculist. When the sight was recorded as 20/20 for both eyes and no notes made as to existing abnormalities, the eyes were considered and are here recorded as normal (table 2). A note was made in the history of whether or not glasses were worn. The group with pathologic tonsils had the highest percentage of normal sight, 59.7 per cent, 30.6 per cent wore glasses. Those with normal tonsils had the next highest percentage of normal sight, 56.5 per cent, 33.4 per cent of them wore glasses. Those whose tonsils had been removed had the poorest sight, only 55.5 per cent having normal vision, 41.5 per cent of this group wore glasses. Those with pathologic tonsils seemed to fare better than did members of the other two tonsillar groups in that they had considerably less astigmatism. The fact that those with pathologic tonsils had the best sight offers a temptation to hunt for an explanation in the fact that tonsillar groups are in themselves selective.

groups Children who have their tonsils removed come in large proportion from native born stock, from health conscious families and from families of better material circumstances rather than from the poorer classes, they are from urban rather than from rural communities, and they have experienced more illness than have either those whose tonsils are normal or those whose tonsils are pathologic It seems possible that the sight of the individuals in the three groups was more affected by the factors that determine the selection of the groups than by the condition of the tonsils

The examination of the ears was somewhat unsatisfactory on account of the number of external ear canals occluded by wax The percentages of ears that were clear and thought to be normal varied between 91.8 per cent and 93.4 per cent, and the difference in percentages in the three groups were without significance (table 2)

There seems to be a positive relationship between the nasal and the tonsillar condition Normal tonsils were associated with the highest incidence of normal nasal cavities (table 2) Persons without tonsils, in turn, fared better in nasal conditions than did those with pathologic tonsils in whom the highest percentages of deviated septums, spurs and evidence of chronic rhinitis were found The differences in percentages are all suggestive, and a number have statistical significance

Teeth—Dental examinations of students entering the university were made by dentists, and careful records were kept of all filled or carious teeth, of absent teeth and of dental appliances Since many of the students examined had not yet erupted the third molars, a separate record of these four possible teeth was made, and they are not included in the table presented Fillings, crowns or cavities in the third molars that were present are not included in counts of damaged teeth (tables 1 and 2)

The number of teeth filled, crowned or with cavities was counted, and listed for all students, regardless of whether teeth were absent or not Nowhere did differences in the three groups appear The data of greatest reliability, especially when combined with those on the number of missing teeth, seemed to be those concerning persons with no teeth absent, and are here presented (table 1)

The mean number of damaged teeth in the three groups differed by amounts that are within the variations of chance No reciprocal relationship between the tonsillar and the dental condition was apparent

Menstrual Characteristics—Menstrual experiences, such as age of onset, duration, amount of irregularity, amount of flow and degree of pain as judged by data gathered from histories taken at the time of the entrance of the students to the university, were remarkably similar in the three groups selected on the basis of the tonsillar condition (table 1)

The only difference in percentages that has value is in the age of onset. Those whose tonsils had been removed menstruated first at 13.17 years, whereas those who had normal and pathologic tonsils menstruated first at 13.28 and 13.29 years, respectively.

Here, as in the case of determinations of the blood pressure, the lack of an established optimum value makes it difficult to determine where health advantage is to be placed, with the earlier establishment of menstruation of those whose tonsils had been removed or with the later establishment of menstruation of the other two groups.

SUMMARY

1 Reference is made to my published paper presenting the relationships existing between the histories of disease, operation and cardiac condition of persons with normal tonsils, persons whose tonsils have been removed and persons with pathologic tonsils. In that paper the source of the material and its method of organization and presentation is described and the related literature reviewed.

2 The physical measurements of height, weight deviation from an arbitrary standard, capacity of the chest, posture, character and number of abnormal vertebral curves, arches of the feet, complexion, presence and distribution of acne, presence of enlarged cervical glands, character of the thyroid, cardiac conditions, heart rate and systolic blood pressure, condition of the eyes, ears and nasal cavities, condition of the teeth and menstrual experiences of young women with normal, absent and pathologic tonsils are here contrasted.

CONCLUSIONS

The outstanding relationships between physical measurements and tonsillar conditions brought out by this study are:

1 The condition of the tonsils, whether normal, absent or pathologic, has little effect on the physical condition of young women of college age from 15 to 35 years.

2 No significant relationship exists between the complexion and the tonsillar condition or between the tonsillar condition and the percentage of palpable cervical glands, the posture, the exaggeration of vertebral curves and the ear and dental conditions.

3 No significant relationship exists between the tonsillar and the menstrual conditions as judged by the mean duration of menstruation in days, the amount of pain, the amount of flow and the amount of irregularity.

4 Those who have had their tonsils removed have less acne than those with pathologic tonsils, who in turn have less acne than those with normal tonsils.

5 A larger number of those with pathologic tonsils than either of the other two groups have thyroid glands with adolescent enlargements

6 Those with normal tonsils have poor feet, as judged by the percentages of those with low and flat longitudinal arches

7 Those with pathologic tonsils have better vision and fewer ocular defects than those with normal tonsils or those whose tonsils have been removed

8 The most perfect nasal structures are found in the group with normal tonsils. Those without tonsils have better nasal cavities than those with pathologic tonsils, in which group are found the largest number of deviated septums

9 Those whose tonsils have been removed attain a mean height of from one tenth to one fifth of an inch greater than those who have kept them

10 The mean weight of those who have pathologic tonsils is greater than that of those without tonsils, whose weight in turn is greater than that of those with normal tonsils

It is suggested that these groups are somewhat determined by such factors as heredity, place of residence, past health history, standards of living and attitude toward medical care, and that these factors are effective and are to some extent responsible for the differences in physical measurements found in the three groups selected on the basis of their tonsillar condition

COMMENT ⁴

The condition of the tonsils is of minor importance in influence on the health history and the determination of physical measurements of young women. Such influence is tangled with that of factors determining whether pathologic tonsils shall be removed or not, and is therefore difficult to evaluate.

The contention that normal tonsils are an aid in resisting disease is not strongly defended by contrasting the histories of disease of those with normal and those with pathologic tonsils. The argument that the removal of tonsils closes a portal of entry for infectious and respiratory diseases is not sustained by a comparative study of the histories of those who have had their tonsils removed and of those whose tonsils are present. The effect of the tonsils as a focus of infection does not find much support when histories and physical measurements of those with pathologic tonsils are contrasted with either those with normal or those with absent tonsils.

⁴ The comment is based on the comparison of histories (footnote 1) as well as on the comparison of physical measurements

The effect of normal tonsils in augmenting growth or of pathologic tonsils in retarding development is not apparent in this study. The effect of the tonsils on the glands of internal secretion is suggested in the thyroid findings, but is not evident in comparative menstrual experiences or in the results of growth. The theory that the tonsillar condition is influenced by diet and reflects nutritional conditions, as may teeth, stature and weight, is not greatly aided by the findings of this investigation.

This study does not emphasize the arguments for the removal of tonsils other than for the cure of a local throat condition. Similar studies at younger and at older age levels should be undertaken to evaluate further the arguments for the removal of tonsils.

PSITTACOSIS

REPORT OF FIVE CASES¹

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AND

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In this communication is presented a household outbreak of five cases of psittacosis running a characteristic course, with definite pathologic as well as biologic evidence substantiating the diagnosis. These followed the importation of a group of love birds or parakeets from Havana.

Parakeet is the name given to certain subgroups of the family Psittacae or parrots¹. It includes especially the parrots of relatively small size and slender form with a long graduated tail, e g, the subfamilies of Palaeonithinae and Platycercinae of Asia, Australia and Polynesia, and the Cornuinae of South and Central America. The latter is still to be found in the southern part of the United States and is sometimes spoken of as the Carolina parakeet.

According to Roubakine,² the disease psittacosis in man is caused, in the vast majority of cases, by the green parrot of the species *Chrysotis amazonicus*. However, he mentioned an epidemic of the disease that occurred in Zulpich, in the Rhineland, in 1909, which was due entirely to the Australian parakeet. In the widespread epidemic of one year ago, mention was made by Anderson³ of cases in which the disease was contracted from canaries. Armstrong⁴ noted parrots, parakeets, love birds and canaries as sources of infection. The experimental work of Rivers, Berry and Rhoades,⁵ in which they succeeded in inoculating parrots, mice, rabbits, guinea-pigs and monkeys with the disease, would seem to indicate that any of these species might be a

¹ Submitted for publication, June 29, 1931.

² From the medical service of Meyer A Rabinowitz, Jewish Hospital of Brooklyn, N Y.

1 Salvadori, A T. Catalogue of Parrots in the Collection of the British Museum, London, Longmans & Company, 1891.

2 Roubakine, A. Monthly Epidemiological Report of the League of Nations 9 141 (April) 1930.

3 Anderson, G W. New England J Med 204 67 (Jan 8) 1931.

4 Armstrong, C. Pub Health Rep 45 2013 (Aug 29) 1930.

5 Rivers, T M, Berry, G P, and Rhoades, C P. Psittacosis. Observations Concerning Experimental Disease in Parrots, Mice, Rabbits, Guinea-Pigs and Monkeys, J A M A 95 579 (Aug 23) 1930.

potential carrier of infection. In addition to the susceptible animals mentioned, Waid and Gallagher⁶ included the pigeon and fowl.

The parakeets concerned in this report were purchased in Havana, Cuba, by one of the patients, Mrs. B., Jr., who gave them to the butcher on board ship to take care of during the return trip to New York City. This is a general practice among tourists bringing pets back to this country. On arrival at New York two of the birds were delivered to a neighbor. Of these two, one was found dead when received, while the other died shortly after reaching the neighbor's home. Neither of these birds gave rise to any cases of psittacosis. Of the four remaining birds, two were given to Mr. B., Sr. (case 1), father-in-law of Mrs. B., Jr. On the first night, Mrs. B., Jr.'s, male bird and Mr. B., Sr.'s, female bird escaped from their cages and were never located. The remaining birds were reared under the care of Mr. B., Sr.

On January 13, nine days after the birds came into his house, Mr. B., Sr., who was very fond of them and himself took care of them, became ill with a very severe pneumonic infection, and died after five days of illness. He was buried on January 19, and, as is the custom in an orthodox Jewish household, the family gathered at the home of the deceased to observe for one week a period of mourning. During this week an intestinal disturbance developed in one of the two remaining birds, and it soon died with a "protruding rectum." All the mourners were exposed to both the sick and the "well" bird. On January 28, nine days after the family group gathered, Mrs. H., sister of Mr. B., Sr., took ill. On February 3, Mrs. G., daughter of Mr. B., Sr., on February 5, Miss S., another daughter of Mr. B., Sr., and on February 8, Miss B., Jr., the importer of the birds, fell sick.

Although the one remaining bird was apparently still healthy, Dr. G. P. Berry of the Rockefeller Institute was able to demonstrate the psittacosis virus in its organs.

For obvious reasons the case reports are markedly abbreviated.

REPORT OF CASES

CASE 1—Mr. B. Sr., aged 65, took ill on January 13, complaining of chills, fever and headache. His temperature rose rapidly to 103.8 F., and on the following day he showed diffuse signs of bronchopneumonia in both lungs. Death occurred on the fifth day of illness.

Owing to the prevalence at that time of a local "influenzal bronchopneumonia" epidemic, and the fact that the patient had previously been suffering from chronic bronchitis, emphysema, severe cardiac failure and hypertrophied prostate, his illness and demise created no suspicion until the other members of the family began to come down

⁶ Waid, A. R., and Gallagher, B. A. Diseases of Domesticated Birds, New York: The Macmillan Company, 1920.

with pneumonic disease. At this time a common etiologic factor was looked for, and at once suspected as psittacosis infection because of the history of the parakeets.

CASE 2—Mrs. H., aged 51, obese, on January 28 began complaining of chilly sensations, fever and malaise, and later of palpitations. She was admitted to the Jewish Hospital (as were the subsequent patients) on February 5, extremely ill, prostrated, toxic and cyanotic, with a distressing hacking cough, but absolutely no expectoration. There were signs of extensive patchy pneumonic involvement of both lungs. The temperature ran an extremely high, flat, plateau-like course. The respirations were very rapid. A typhoidal state soon developed, with low muttering delirium, distressing abdominal distention and persistent, extremely foul loose, watery diarrhea. Examination of the stool for typhoid bacilli proved negative. The pulse became irregular, and death occurred on the seventeenth day of illness. Examination by Dr. G. P. Berry of the blood and sputum of the patient taken on the thirteenth day of the illness failed to reveal the presence of the psittacosis virus. However, it was successfully demonstrated in the liver, lungs and spleen removed at autopsy.⁷

Important anatomic data were: lobular pneumonia, thrombosis of the pulmonary artery, pulmonary veins, iliac vein and splenic vein, gastro-enteritis, and multiple hemorrhages of the spinal cord with chromatolysis, satellitosis and fat replacement of the anterior horn cells.

CASE 3—Mrs. G., aged 40, became ill on February 4, complaining of pain in the back below both scapulae and malaise. Her temperature was 101 F. During the following two days she experienced repeated chilly sensations, and her temperature rose to 103.8 F. On February 7 she was admitted to the Jewish Hospital, extremely ill, toxic, prostrated and complaining of severe pain in the left side of the chest, anteriorly and posteriorly, and of a hacking unproductive cough. Examination of the chest gave negative results. Severe headache, marked apathy and listlessness were present throughout. On the seventh day of the illness, numerous extremely fine crepitant râles were heard in the right side of the chest, and roentgen examination confirmed the impression of incomplete consolidation of the upper lobe of the right lung. The temperature gradually fell to normal on the twelfth day of the illness. The hacking cough persisted with very scant mucoid expectoration. On the seventh day the patient had a severe diarrhea consisting of five loose watery stools, not foul in nature. After two days of normal temperature, the patient went into collapse from a pulmonary embolus. With prompt and continuous use of the oxygen tent, she gradually rallied. The rally was followed by evidence of thrombosis of the left saphenous vein. Sputum and blood taken on the seventh day of the illness for examination for the psittacosis virus proved negative.

CASE 4—Mrs. S., housewife, aged 37, became ill on February 5, complaining of chilliness, feverishness and weakness. On the following day, her temperature was 102 F. On February 7, a severe throbbing right-sided headache developed. The patient was moderately prostrated and slightly cyanotic. The lungs were apparently clear.

There was no cough. The tongue was grayish brown with clear edges. The patient's mental condition was good, but the headache was extremely distressing.

⁷ A detailed report of the autopsy observations is given by Polayes, S. H., and Lederer, M. Psittacosis, Postmortem Examination of a Case, Including Studies of the Spinal Cord, *Arch. Int. Med.* 49:253 (Feb.) 1932.

On February 11, fine crepitant râles were heard at the base of the right lung posteriorly, and on the following day a roentgenogram revealed an area of dense, sharply demarcated consolidation just above the middle of the right pulmonic field peripherally. On February 18, the left lung showed signs which soon involved the entire lung. The temperature curve showed two distinct cycles. On March 5, pain and tenderness developed in the left calf, which were interpreted as evidence of deep venous thrombosis. Specimens of the sputum and blood taken on the sixth day of the illness proved negative for psittacosis virus.

CASE 5—Mrs B, Jr, aged 32, was admitted to the Jewish Hospital on February 8 following an illness of only one day. This began with chilly sensations, high fever and an exacerbation of a preexisting cough. She was moderately prostrated, not markedly cyanotic, but had a harsh cough with occasional blood-tinged expectoration. The signs in the chest showed great tendency to vary from day to day, most râles being extremely fine. A roentgenogram of the chest on February 12 revealed an area of dense consolidation in the upper field of the left lung. The temperature showed two distinct cycles, falling to normal by the twenty-first day of illness. Headache was not a prominent feature in this case, and there was neither diarrhea nor clinical evidence of thrombosis. The cough was especially distressing. A smear of the sputum showed scanty cytology, consisting chiefly of lymphocytes with an occasional polymorphonuclear neutrophil, a few large epithelial cells, a moderate number of large cells with pale nuclei and pale pink protoplasm and a few red blood cells. Examination of the sputum taken on the third day of illness definitely demonstrated the presence of the psittacosis virus. The virus could not be found in the patient's blood taken at the same time.

HISTORICAL REVIEW

The first description of psittacosis to be found in the literature is that of Ritter⁸ who described an epidemic that occurred in Switzerland in 1879. This consisted of seven cases of a severe atypical pneumonia or "pneumo-typhus," with three deaths. The epidemic was attributed by Ritter to a shipment of parrots recently received from Hamburg. Since that time numerous reports of small epidemics of a similar nature have appeared, but it was not until the large Paris epidemic of 1892-1895 that Morange gave the disease the name psittacosis from the Greek *ψιττακός* meaning parrot. This Paris epidemic consisted of seventy-eight cases with twenty-four deaths, and was caused by the importation of five hundred birds from the Argentine.

The first report of psittacosis in this country was in 1904, when Vickery and Richardson⁹ reported three probable cases. Scott¹⁰ in 1906 recorded three cases. The next report was in 1917 by McClintock¹¹ who described thirteen cases in Wilkes-Barre, Pa., with only one death. In 1929, the report of a single case with recovery was published by Sailer¹² in Philadelphia.

8 Ritter, J. *Deutsches Arch f klin Med* **25** 53, 1879.

9 Vickery, H. F., and Richardson, O. *Tr Am Physiol Soc* **19** 364, 1904.

10 Scott, H. N. *Tr New Hampshire M Soc*, 1906, p 168.

11 McClintock, A. T. *Arch A T McClintock Mem Found* **1** 1, 1925.

12 Sailer, I. *M Clin North America* **12** 1095 (Jan) 1925.

In 1930, there was the great pandemic that started in the city of Cordoba, Argentine,¹³ and involved in its spread continental Europe, England,¹⁴ the United States,¹⁵ Canada and Hawaii. Approximately five hundred cases were reported within a period of one year.¹⁶ In this country, Armstrong⁴ recorded the occurrence of one hundred and sixty-nine cases from Nov 23, 1929 to May 7, 1930. Since this time there have been reports of many cases from numerous sources and in all parts of the country. These total approximately sixty-five cases.¹⁷

CLINICAL FEATURES

The disease was insidious in its onset, beginning with chilly sensations, malaise and fever. However, in one case there was a sudden onset, with an abrupt rise of temperature to 104 F. Cough was usually present, but was not prominent except in one case. A characteristic feature was the extremely thick, mucoid expectoration, occasionally blood-tinged. This tenacious sputum is in keeping with the microscopic appearance of the lung post mortem, i. e., the prominent network of interlacing fibers of fibrin which sometimes completely fill the alveoli.

A diagnosis of grip or influenza is often made. In our cases we were impressed by the absence of the extremely hyperemic oropharynx seen in "influenza."

Pulmonary signs may not appear until the disease is well advanced. In two cases there were two distinct cycles of the disease, the second appearing with the involvement of a new pulmonary area. An important finding is the persistent, very fine crepitant râles in the involved area. The absence of any evidence of pleuritic involvement, clinical or pathologic, in the presence of extensive pulmonary pathologic involvement, is in keeping with the findings of MacLachlan, Permar and Rogers.¹⁸

13 Barros, E. *Rev Asoc med argent* **43** 17 (Jan-April) 1930, abstr, *Lancet* **1** 472 (March 1) 1930.

14 Thomson, A. P., and Hillier, W. T. *Lancet* **1** 396 (Feb 22) 1930.

15 Anderson (footnote 3) Armstrong (footnote 4) Peterson, E., Spalding, O. B., and Wildman. Psittacosis. A Clinical and Roentgenologic Study of Seven Cases with Postmortem Observations in One Case, *J A M A* **95** 17 (July 19) 1930. Bortz, E. L., and Green, B. Psittacosis, *J A M A* **95** 400 (Aug 9) 1930. Rivers, T. M., Benjamin, B., and Berry, G. P. Psittacosis, Report of a Case, *J A M A* **95** 577 (Aug 23) 1930. Wellman, H. E. *New England J Med* **203** 421 (Aug 28) 1930. Sandoer and Coburn. *J Kansas M Soc* **31** 280 (Aug) 1930. Kahn, T. F., Jr. *Yale J Biol & Med* **2** 417 (July) 1930. Haines, H. G. Psittacosis, Study of Three Cases, *J A M A* **94** 1821 (June 7) 1930. Reisman, D., and Davidson, H. S. *M Clin North America* **14** 815 (Jan) 1931.

16 Wellman, H. E. *New England J Med* **203** 421 (Aug 28) 1930.

17 Gorham, L. W., Calder, F. G., and Vedder, J. D. Psittacosis, Report of Five Cases, *J A M A* **94** 1816 (June 7) 1930.

18 MacLachlan, W. W. G., Permar, H. H., and Rogers, C. A. *Ann Int Med* **4** 260 (Sept) 1930.

One prominent feature of the disease was the tendency to thrombosis. There was no change in the bleeding or coagulation time in any case. Thrombi were found post mortem in the pulmonary vessels, right iliac vein and splenic vein in case 2. In case 3, a pulmonary embolus was the first indication of an extensive thrombosis of the veins of the left leg. In case 4, there was evidence of deep peripheral venous thrombosis. It would be well to bear this feature of the disease in mind, both from a therapeutic and a prognostic point of view. Mention of thrombophlebitis as a common complication was made by Armstrong⁴ in his survey of the epidemic of 1930 in the United States. We also noted a report of two deaths due to pulmonary embolus during an outbreak of psittacosis among the employees of a department store, recorded by Badger¹⁹.

Headache was extremely prominent in two cases, but less marked in two others. It is likely that this has a definite pathologic basis in the marked congestion of the meninges. The spleen was palpated in only one case, and a transient roseolar eruption noted in one. The tongue showed a grayish-brown coat with clean edges in all cases.

The temperature showed wide, daily fluctuation in most cases, but in one fatal case (case 2) assumed the plateau-like fastigium. The pulse and respirations were in no way distinctive. The leukocyte count was characteristically but slightly increased, ranging between 9,000 and 13,000, with a percentage increase of the polymorphonuclear cells. In all cases eosinophilic leukocytes were found on at least one occasion during the active phase.

The ages of our patients varied from 32 to 65. The two fatalities occurred in the older persons, who also happened to be the first to be affected. The diminished resistance of the elderly patient to this disease as compared to the more youthful one has been pointed out by Horder and Gow²⁰. In the older person, the disease runs an extremely rapid, fatal course, while in the younger patient it may be relatively innocuous and mild.

The incubation period of the disease is rather clear in two of our cases. In cases 1 and 2 a definite period of nine days between the first exposure and the appearance of symptoms is demonstrable.

SUMMARY

1 Five cases of psittacosis occurring in one family are presented, with autopsy observations in one.

2 The disease in these cases is distinctly attributable to exposure to infected love birds or parakeets brought to this country from Havana,

19 Badger, L. F. Pub. Health Rep. **45** 1403 (Feb. 1) 1930.

20 Horder, T., and Gow, A. E. Lancet **1** 237 (Feb. 1) 1930.

Cuba, by returning tourists. This is of extreme epidemiologic and diagnostic importance.

3. Biologic evidence of the identity of the disease was possible in this epidemic, the virus of psittacosis being clearly demonstrated (*a*) in the sputum of one of the patients (case 5), (*b*) in the liver, lung and spleen of another (case 2) and (*c*) in the liver and spleen of the only bird available for examination. That this bird was apparently healthy is of great epidemiologic importance.

4. The characteristic clinical points of diagnostic importance are (*a*) History of exposure to a diseased bird. (*b*) Incubation period of approximately nine days. (*c*) Marked headache. (*d*) Toxemia which may be decidedly out of proportion to the physical findings in the chest. (*e*) Slight cough with extremely scanty, thick, tenacious expectoration which may or may not be blood-tinged. Further observation is necessary to determine whether microscopic study of the sputum (case 5) is characteristic of the disease. (*f*) An extremely fine type of crepitant râle. (*g*) Roentgen evidence of dense consolidation of part of a lobe of the lung almost from the very onset of symptoms. (*h*) No pleuritic involvement in the face of extensive pulmonary pathologic involvement. (*i*) Moderate or no leukocytosis in the presence of severe pneumonic infection. (*j*) Tendency to venous thrombosis.

CHOREA GRAVIDARUM

A STATISTICAL STUDY OF 951 COLLECTED CASES, 846 FROM THE
LITERATURE AND 105 PREVIOUSLY UNREPORTED *

PRENTISS WILLSON, M D

AND

ALEC A PREECE, M D

WASHINGTON, D C

In the summer of 1925 the attention of one of us (Dr Willson) was directed to the complication of pregnancy with chorea by the opportunity to study a case and to treat the patient in his private practice. The patient recovered, but was so desperately ill and presented such a terrifying picture at the height of the disease that she aroused the greatest interest in all who saw her. A cursory examination of the literature undertaken at the time she was under treatment made it obvious that chorea gravidarum was a serious and very rare condition, with an estimated mortality of approximately from 25 to 33.33 per cent, and that there was absolutely no unanimity of opinion as to its true character, and hence, naturally, no accepted therapeutics, particularly with reference to the question of the necessity for interrupting pregnancy. These findings have led us to avail ourselves of the opportunity afforded by the report of this case to present a complete and comprehensive study of the whole subject. Obviously, in order to be of value, such a survey of any medical condition must present a composite picture of the disease, based on many observations, clearly demonstrating all its possible variations in course, duration, severity, complications, etc. In no other way are sound generalizations on the subjects of etiology, pathology, prognosis and treatment possible. When the disease under investigation is one as rarely seen as chorea gravidarum, the opportunity to observe which, even in the material of a large clinic, may not occur for years, the only feasible approach to the problem would seem to lie in collecting the largest possible number of cases from the literature and any other available sources in order that their data may be subjected to critical analysis. With this end in view, a thorough search of the literature to Sept 30, 1930, was undertaken, and, in addition, 530 questionnaires were sent to the members of several American obstetrical societies with the result that this paper is based on the analysis of the more or less detailed reports of 1 personal case, of 846 choreic pregnancies, occurring in 711 patients, reported in the literature, and of 104 choreic pregnancies,

* Submitted for publication, June 18, 1931

† The cases from the literature include those published to Sept 30, 1930

occurring in 85 patients, reported by those replying to the questionnaire, thus assembling for study a total of 951 choreic pregnancies in 797 persons. This material has been abstracted in tabular form in table 1 under the following captions: Age, social status (married or single), parity, previous history of chorea, previous history of rheumatism, evidence of cardiac disease, month of pregnancy in which chorea had its onset, duration of attack, fate of the pregnancy, result to mother, result to child and comment (autopsy observations, notes on treatment, condition of urine, blood pressure, blood picture, etc.)

Since the main purpose of this communication is to throw as much light as possible on the matter of the true character of chorea gravidarum, it has seemed best to us to present the subject in the following order. First we shall report our own case. Then we shall present a review of the history and literature of the disease, with special attention to a résumé of the opinions that have been entertained with respect to its true nature. We will then give the opinion that we have formed on this point as the result of our study. The various analyses of the collected data will then be considered in detail under the usual headings of frequency and geographical distribution, etiology, pathology, clinical course, symptoms, complications, diagnosis, prognosis and treatment. In each instance, the consideration of these subsidiary topics will be concluded by giving the interpretation of the findings that has led us to form our opinion on the nature of the disease. In conclusion, we shall present a brief summary of the whole subject.

REPORT OF CASE

On July 24, 1925, Mrs. L. M., aged 20, a primipara, who was four months pregnant, first came under observation. The family history was unimportant. The patient had had the usual diseases of childhood, with the exception of scarlet fever and diphtheria. The previous history was otherwise irrelevant, except for the statement that she had been "nervous." The menstrual history was normal. The pregnancy was normal, with no nausea or vomiting. Physical examination disclosed a tall, very well nourished and developed girl of good color, her usual weight was 130 pounds (59 Kg.). There were no devitalized teeth, but a few with cavities. The tonsils were not diseased. There was a slight systolic blow at the apex, but no evidence of cardiac disease, the blood pressure was 110 systolic and 56 diastolic.

The patient was next seen on August 14, when the blood pressure and urine were again normal. She complained of being "nervous," but appeared to be in perfect health. On August 25, the patient was again seen, and a diagnosis of chorea could be made when she entered the room. She was constantly twitching, jumping and grimacing, and the picture was altogether typical. At this time it first developed that the "nervousness" mentioned in her history had been a definite attack of chorea for which she had been treated by Dr. Noble P. Barnes two years previously, when she was 18 years of age. The patient was put to bed at home for a week, but, as there was no improvement, she was admitted to Columbia Hospital for Women on September 2 for observation and treatment.

At this time the condition was not alarming, except for the gloomy prognosis given in every textbook consulted. While the patient was awake, the movement was constant and general, but ceased during sleep. The patient was cheerful and not greatly alarmed. Dr. Barnes saw her with us and directed the medical treatment, which consisted of rest, a light diet, regulation of bowel function, triple bromides by mouth and large doses of salicylates by rectum. On September 9, sodium cacodylate was given intramuscularly, and on the eleventh, 0.9 Gm. of neoarsphenamine intravenously, morphine was given as needed. The condition, however, became slowly but progressively worse. The movements were more violent, and incoordination was so extreme that the patient could not feed herself, after attempting to do so, her bed would be surrounded by portions of food that had been thrown on the floor. Insomnia was troublesome, her morale became very low, and her body from head to foot was covered with bruises where she had struck herself on the bed. The movements were so violent that one of the attending physicians, seeing her for the first time, mistook the condition for an eclamptic convulsion. On September 14, we asked Dr. D. V. D. Stuart to see her with us, and he made the following notations on the chart:

"This patient presents

"(1) Violent choreiform movements involving apparently all the voluntary musculature of the body excepting the external ocular muscles

"(2) Pressure points of tenderness along course of left radial, circumflex, great sciatic and posterior tibial nerves. There is no demonstrable weakness of any of the muscle groups innervated by the above nerves

"Impression—choreiform condition, not hysterical, due to the patient's pregnancy

"Suggest termination of pregnancy"

Acting on this advice, a Wales bougie was introduced at noon on September 14, the pregnancy being then advanced to 5½ months. Labor was slow in starting and delivery of a stillborn fetus did not occur until 3:30 p. m. on the sixteenth. It would be impossible to exaggerate the pitiable and terrible condition of this girl during the interval. She was placed in a padded bed from which she could not throw herself. No clothing could be kept on her, and most of the time she was stark naked. The movement was constant and violent to an unbelievable degree, at least a foot in the air at one moment, on her heels and occiput at the next, and at the next with her feet over her head banging against the head of the bed, inarticulate animal-like cries her only means of expression, deglutition almost impossible even for water, and yet quite conscious, she made an indelible impression on all who saw her.

The postpartum progress was shown by notations by Dr. Stuart as follows: September 19. "Patient's condition is not materially changed since induction of labor. There is less involvement of tongue and pharyngeal muscles than when first seen but choreiform movements are still general. Tenderness over nerve trunks, noted at first examination, is still present." September 24. "Choreiform movements much less marked. There is still some tenderness over course of left radial nerve and left posterior tibial, other nerve trunk tenderness has disappeared." From this time on improvement was steady and rapid, and the patient was discharged on the twenty-seventh. One month later, all movement had ceased, and one year later the patient presented the picture of health. We have just been informed, however, that the patient has recently had a mild recurrence of the chorea unassociated with pregnancy.

The whole course of the disease was afebrile with the exception of a transitory temperature of 102.4 F., three hours before delivery. The pulse range during hos-

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Chorea Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five-Hundred and Thirty American Obstetricians*

For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status†	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea‡	Time of Recovery from Chorea§	Date of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
1	1	Reidlin, 1696				Yes					Spontaneous labor at term	L	D	
2	2	Ungen, 1764	18		I				5	A p in ninth month	Spontaneous labor at term	L		
3	3	Hand, 1807	23	S	I				6	A p	Spontaneous labor at term	L		
4	1	Capuron, 1817	24	M	I					P p	Spontaneous labor at term	L	L	
5	5	Vogel, 1820	22	M	I				3	3 years p p	Spontaneous labor at term	L	D	*Early in pregnancy
6	6	Frank, 1821			I	Yes			*		Spontaneous labor at term	L	D	
7	7	Prehard, 1824									Spontaneous labor at term	D	D	Autopsy cerebral congestion
8	8	Jeffreys, 1825	17	M	I				2	A p in fourth month	Spontaneous labor at term	L		
9	9	Turner, 1838	23	M	I				2	A p	Spontaneous labor at term	L		*First half of pregnancy
10	10	Beard, 1839	19	M	I				*		Spontaneous labor at term	L		
11	11	Ingleby, 1840			I	Yes			6	A p in ninth month	Spontaneous labor at term	L		
12	12	Ingleby, 1840							4	P p	Spontaneous labor at term	L		
13	13	Ingleby, 1840							*		Spontaneous labor at term	L		
14	14	Ingleby, 1840							*	Until death	Died undelivered	D	D	*Early in pregnancy
15	15	Ingleby, 1840									Spontaneous labor at term	D	D	*Early in pregnancy, ovum of third month found in uterus
16	16	Ingleby, 1840									Spontaneous labor at term	D	D	
17	17	Ingleby, 1840							9	Until death	Spontaneous pre mature labor at term	D	D	Autopsy negative
18	18	Lee, 1842	23		II		Yes				Spontaneous labor at term	L		Tright, died 47 hours post partum, autopsy vegetations on the heart valves
19	19	Trousseau, 1846	17	S	I	Yes			2	A p in fifth month	Spontaneous labor at term	L	L	
20	20	Lever, 1847			I				3	A p in fourth month	Spontaneous labor at term	L	L	

21	21	Lever, 1847	20	III	Yes		*	P p	Spontaneous labor at term	L	*Chorea developed after miscarriage in fifth month of second pregnancy and was present when third pregnancy began
22a	22	Lever, 1847	19	M	No		3	1 month p p	Spontaneous labor at term	L	Chorea improved immediately post partum
b	23	Lever, 1847		M	Yes		*	2 weeks p p	Spontaneous abortion in fourth month	L	*Before third month, fright supposed to have caused abortion
23	24	DuBois, 1848	19		No		2	A p	Spontaneous labor at term	L	
24	25	Helft, 1848	20	S	Yes		1	P p	Spontaneous abortion in fifth month	L	Fright preceded attack
25	26	Helft, 1848	23	M	II		3	P p	Spontaneous labor at term	L	
26a	27	Lever, 1848	24	M	II		5	Until labor	Spontaneous labor at term	L	Chorea ceased with first labor pains and did not recur
b	28	Lever, 1848		M	*	Yes		P p	Spontaneous labor at term	L	*Multipara, chorea less severe in this pregnancy
27	29	See, 1850	20	M	I	Yes	3	A p in sixth month		L	No chorea in a subsequent pregnancy
28	30	Sée, 1850	20	M	I	Yes	9	A few days p p	Spontaneous labor at term	L	Pain in wrists during the attack of chorea
29	31	Sée, 1850					3	Until death	Spontaneous labor at term	L	
30	32	Arnold, 1851	20	M	II	No	3	Until death	Spontaneous labor at term	D	Fright preceded attack, fever, autopsy negative
31	33	Romberg, 1851	20	S	I	Yes	1	6 weeks p p	Spontaneous abortion in sixth month	L	
32	34	Romberg, 1851	23	M	II	No	2	P p	Spontaneous labor at term	L	
33a	35	Romberg, 1851	18	M	I	Yes	*	A p in fifth month	Spontaneous labor at term	L	*Early in pregnancy
b	36	Romberg, 1851	19	M	II	Yes	*		Spontaneous labor at term	L	*Second half of pregnancy, chorea did not recur in third pregnancy
34	37	Anderson, 1853	18		I	Yes	8	2 weeks p p	Spontaneous labor at term	L	Fetal death due to breech presentation
35	38	Duncan, 1854	33	M	I	Yes	4	A p in eighth month	Spontaneous labor at term	L	No albuminuria, chorea limited to lower extremities
36	39	Duncan, 1854	*	M	*		No	A p *	Spontaneous labor at term	L	*Middle aged woman, *multipara *at attack lasted twenty days, no albuminuria, choreiform movements limited to lower limbs and at night only
37	40	Austin, 1855		I	Yes		7	Until death	Spontaneous labor at term	D	Death three days after onset of chorea and twenty four hours post partum eclampsia?
38	41	Austin, 1855			Yes				Spontaneous abortion in seventh month	D	
39	42	Seanzoni, 1855	24	M	I		4	P p	Spontaneous labor at term	L	Chorea ceased after removal of pieces of placenta
40	43	Spiegelberg, 1858	28	M	II	No	*	P p	Spontaneous labor at term	L	*Middle third of pregnancy, chorea ceased immediately post partum, but recurred six weeks later

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41	41	Brannock, 1859	20		I	No			5	P p	Spontaneous labor at term	L		
42	45	Marcé, 1860	22		I				*	*	Spontaneous labor at term	L	L	*Chorea present before pregnancy began and continued post partum
43	46	Levick, 1862	35		V	No			4		Spontaneous labor at term	L	L	
44	47	Levick, 1862	17	M	I	Yes			3		Spontaneous abortion	L	D	Fright preceded attack
45	48	Levick, 1862	17	S	I	No		Yes	5	Until death	Died undelivered in sixth month	D	D	Autopsy cerebral congestion and diseased heart valves
46	49	Mosier, 1862	21		II	Yes			3	P p	Spontaneous labor at term	L		
47	50	No name 1862	26	M	III			Yes	2	Until death	Died undelivered in fourth month	D	D	Autopsy diseased mitral valve
48	51	Snyers, 1863	19		II	No	No		3	A p in fourth month	Spontaneous labor at term	L		
49	52	Kirkes, 1863	20	M	II	No	No	Yes	4	Until death	Spontaneous abortion in fifth month	D	D	Autopsy diseased heart valve
50	53	Kirkes, 1863	25		II	Yes	Yes	Yes	9	Until death	Spontaneous labor at term	D	L	Chorea began four days ante partum, death five days post partum, autopsy congestion of meninges, endocarditis, first pregnancy normal Death due to postpartum eclampsia
51	54	Nagel, 1863	18						8	Until death	Spontaneous labor at term	L		No albuminuria
52	55	Ladé, 1863	23	M	I	No	No		1	A p in sixth month	Spontaneous labor at term	L		Chorea complicated by acute rheumatism and acute endocarditis
53	56	Chambers, 1864	23	M	I	Yes	Yes	Yes	6	P p	Spontaneous labor at term	L	L	Chorea recurred slightly post partum, no albuminuria
54	57	Woodman, 1865	18	M	I	Yes	Yes	Yes	1	A p in fifth month	Spontaneous pre mature labor in eighth month	L		Tight preceded attack
55	58	Woodman, 1865			I				2	A p	Spontaneous pre mature labor in eighth month			
56	59	Hine, 1865	21		II	Yes	No	No	8	Until death	Spontaneous pre mature labor in eighth month	D	L	Emotional disturbance preceded onset of chorea, autopsy negative

57	60	Kunsehert, 1865	21	M	II	Yes	No	3	A p in fourth month	Spontaneous labor at term	L	L	
58	61	Kunsehert, 1865	26	M	IV	Yes	*	9	Untl death	Died undelivered in ninth month	D	D	*Chorea occurred during course of acute rheumatic attack complicating pregnancy, death evidently due to acute nephritis after repeated and prolonged chloroform narcosis
59	62	Fischl, 1865	25	M	III	No	No	3	3 days p p	Induced abortion in fourth month	L	D	Urine normal
60a	63	Dumont, 1865		M	I	Yes	No				L		Mild attack
b	64	Dumont, 1865	22	M	II	Yes	No	5	A p in sixth month		L	L	Attack cleared up after three weeks of treatment
61a	65	Gubler and Dumont, 1865		M	I	Yes	Yes				L		
b	66	Gubler and Dumont, 1865	22	M	II	Yes	Yes	5	A p in sixth month	Spontaneous labor at term	L		
62	67	Jacoud, 1867	23	M				3	A p in fifth month		L		
63	68	Tuckwell, 1867	24				Yes	1	Untl death	Died undelivered in fourth month	D	D	Autopsy negative except for diseased heart valves
64	69	Ogle, 1868	17	S	I	No	Yes	1	Untl death	Died undelivered in fourth month	D	D	Autopsy diseased heart valves
65	70	Ogle, 1868						3		Died undelivered	D	D	Autopsy congestion of meninges of spinal cord
66	71	Ogle, 1868	23	M	II			6		Spontaneous abortion in sixth month	D	D	Death one day post partum, autopsy negative
67	72	Trousseau, 1868	20			No			A p		L		Attack lasted twenty seven days and was complicated by mental disturbance
68	73	Bedford, 1868	19	M	I	No		4	P p	Spontaneous labor at term	L	L	
69a	74	Thompson and Davis, 1868	18	M	I	Yes	No				L		
b	75	Thompson and Davis, 1868	20	M	II	Yes	No	6	3 weeks p p	Spontaneous premature labor in seventh month	L		
70a	76	Tait, 1868	24		I	Yes	Yes	4	P p	Spontaneous labor at term	L	L	Chorea ceased immediately post partum
b	77	Tait, 1868			II	Yes	Yes	*	P p *	Spontaneous labor at term	L	L	*Chorea began before fourth month and ceased immediately post partum
c	78	Tait, 1868			III	Yes	Yes	*	P p *	Spontaneous abortion in third month	L	D	*Chorea began before third month and ceased immediately post partum
d	79	Tait, 1868	27		IV	Yes	Yes	1	Untl death	Induced abortion in fourth month	D	D	No albuminuria, autopsy negative except for congestion of brain
71a	80	Barnes, 1869		M	II	Yes					L	D	No chorea in first pregnancy
b	81	Barnes, 1869	20	M	III	Yes	No	5	P p	Induced premature labor in seventh month	L	L	Puerperal mania developed, which persisted
72	82	Barnes, 1869 (Hufeland)	19				*	7			L		*Chorea followed by acute rheumatism
73	83	Barnes, 1869 (Hufeland)					*				L		*Chorea complicated by acute rheumatism
74	84	Barnes, 1869 (Furnes)						3	A p *		L		*Chorea lasted twenty seven days
75	85	Barnes, 1869 (Mayo)						4	A p in sixth month	Spontaneous labor at term	L	L	*Fright preceded attack, baby had chorea at birth

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76	86	Barnes, 1869 (Pye Smith)	23	M	II			*			Spontaneous labor at term	L		*Late in pregnancy, fright preceded attack
77	87	Barnes, 1869 (Woodman)	20	M	I	Yes	No	Yes	7	2 months p p	Spontaneous labor at term	L	L	
78	88	Barnes, 1869 (Woodman)	18		I			Yes	8	Until death	Spontaneous labor at term	D	D	Albuminuria throughout pregnancy, eclampsia
79	89	Davis, 1869	20	M	I	No	No	?	2	P p	Spontaneous abortion in fifth month	L	D	
80	90	Goodell, 1870	19	M	I	Yes	Yes	No	5	Until death	Accouchement facile in eighth month	D	D	No albuminuria
81	91	Russell, 1870	21	M	I	No			1					
82	92	Weber, 1870	33	M	V	No	No		9	9 days p p	Spontaneous premature labor in ninth month	L	L	
83	93	Steckel, 1870	23	M	III	Yes			*	A p		L		*Middle of pregnancy, first and second pregnancies were normal
84	94	Steckel, 1870	26	M	I	No	No		7	P p	Spontaneous labor at term	L	L	Second pregnancy was normal
85 ^a	95	Steckel, 1870	27		I				6	A p in ninth month	Spontaneous labor at term	L	L	
b	96	Steckel, 1870	30		II	Yes			6	P p	Spontaneous labor at term	L		
86	97	Barnes, 1873	18		I	Yes			3					Fright preceded the attack
87 ^a	98	Barnes, 1873	*		I	Yes	Yes	*	*		Spontaneous labor at term	L	L	*Patient under 20 years of age, chorea developed early in pregnancy
b	99	Barnes, 1873	*		II	Yes	Yes	*	*			L	L	*Patient under 22 years of age, chorea developed early in pregnancy
c	100	Barnes, 1873	22		III	Yes	Yes	?	2					
88	101	Arnold, 1873	19		II	Yes			8	Until death	Spontaneous premature labor in ninth month	D	D	First pregnancy normal
89	102	Bumberg, 1873	36	M	IV			Yes	3	Until death	Died undelivered	D	D	First, second and third pregnancies normal death sixteen days after onset of chorea, autopsy disclosed heart valves

90	103	Prentiss, 1874	25	M	II	No	No	5	A p in eighth month	Spontaneous labor at term	L	L	
91	104	Prentiss, 1874	25	M		No	No	4	A p in eighth month	Spontaneous labor at term	L	L	
92	105	Mackall, 1874	18	S	I	No		*	Until death	Died undelivered	D	D	*Onset of chorea when several months advanced in pregnancy
93	106	Fehling, 1874	23		I	No		7	3 weeks p p	Spontaneous premature labor in eighth month	L	D	
94a	107	Ellscher, 1871	20		I	Yes		6		Spontaneous labor at term	L		For report of autopsy see text
b	108	Ellscher, 1874	22		II	Yes		5	Until death		D		Slight albuminuria
95	109	Oulmont, 1875	28	M	I	No	Yes	?	A p in fourth month		L		
96	110	Oulmont, 1875	25		I	No	Yes	1	A p	Spontaneous labor at term	L	L	
97	111	Fasbender, 1875	23		I	No	Yes	9	P p	Died undelivered	L	L	
98	112	Prince, 1875	20	M	I			4	Until death		D	D	Death three days after onset of chorea, morphine, 1 grain, given, death due to morphine?
99	113	Simpson, 1875	20	S		Yes	No	3	Until death		D	D	Death in fifth month of pregnancy, autopsy negative
100	114	Schwechten, 1876	24		I	Yes		*	P p		L	L	*Chorea since 7 years of age, present when pregnancy occurred
101	115	Schwechten, 1876	22	M	I	Yes		*	A p	Spontaneous labor at term	L	L	*Onset of chorea in first half of pregnancy
102	116	Schwechten, 1876	19		I	Yes		6	A p		L	L	
103a	117	Schwechten, 1876 (Fieber)			I	Yes		*	A p		L	L	*Early in pregnancy
b	118	Schwechten, 1876 (Fieber)	23		II	Yes		2	A p in third month		L		
104	119	Dickinson, 1876	17	S		No	No	Yes	1	Until death	D	D	Autopsy cerebral congestion and mitral disease
105	120	Lyman, 1877	30	S		Yes		2			L		
106	121	Lyman, 1877	18	S		Yes		*	P p *	Spontaneous labor at term	L		*Chorea was present when pregnancy occurred, but ceased immediately post partum
107	122	Richardson, 1877	17		I	Yes					L		No chorea in first pregnancy
108	123	Richardson, 1877	22		II	Yes		6	5 days p p	Spontaneous labor at term	L	L	*Chorea developed late in pregnancy and persisted for months post partum
109	124	Hazard, 1877	22					*	P p *	Spontaneous labor at term	L	L	
110	125	Hazard, 1877		S		No		9	3 weeks p p	Spontaneous labor at term	L	L	
111	126	Swift, 1878	23	S	I	Yes		2	Few days p p	Spontaneous labor at term	L	L	
112	127	Edgerly, 1878	24	*	II	No	Yes	3	A p in fifth month	Spontaneous labor at term	L	L	*Patient was married, pregnancy was illegitimate, however
113	128	Edgerly, 1878	19	S	I	Yes	Yes	1	P p	Spontaneous labor at term	L	L	
114	129	Hamilton, 1878	24					6	3 weeks p p	Spontaneous labor at term	L	L	Fright
115	130	Wade, 1880	19	S	I	Yes	?	6	P p	Spontaneous labor at term	L	L	Cervix dilated twice, under chloroform, in the seventh month, to cure the chorea, which was better but persisted until post partum

130a	150	Bernicke, 1883					P p	L	*Multipara
b	151	Bernicke, 1883	*	Yes			P p	L	*Multipara
c	152	Bernicke, 1883	*	Yes			P p	L	*Multipara
d	153	Bernicke, 1883		Yes			P p	L	*Rheumatism complicating the chorea
131	154	Perego, 1883	25 M	*		2	A p in seventh month		
132	155	Muleur, 1884	*	I	Yes	No	Until death	D	*Patient between 18 and 20 years of age, *Onset of chorea early in pregnancy, autopsy negative
133	156	Brouardel, 1884	18	I	Yes	No	A p in seventh month	L	
134a	157	Olshausen, 1884	21 M	I	Yes		Spontaneous labor at term	L	
b	158	Olshausen, 1884	23 M	II	Yes	Yes	Induced labor in ninth month	D	*Onset of chorea early in pregnancy, continuous chloroform narcosis for twenty-four hours, autopsy effusion under arachnoid, pneumonia
135	159	Stephann, 1885	21 23 M	I *		9 5	Until death	D	*Multipara, death about one week after onset of chorea, mania, high fever
136	160	Miles, 1885					P p	L	
137a	161	Young, 1885		M I	Yes		Spontaneous abortion in sixth month	D	
b	162	Young, 1885	23 M	II	Yes	1	Spontaneous labor at term	L	
138	163	Churton, 1886	24 S			3	A p	L	Emotional disturbance preceded attack
139	164	Churton, 1886	20 M		Yes	2	P p	L	
140	165	Churton, 1886	22		Yes	3	Few days p p	L	
141	166	Churton, 1886	23 S	I			Until death	D	Patient moribund at time of operation, died at once, no albuminuria
142	167	Charles, 1886	20 S		No	1	5 weeks p p	L	
143	168	Pollock, 1886							
144	169	Litten, 1886		I	Yes	3			Acute rheumatism immediately before onset of chorea
145	170	Litten, 1886	23 M	II	Yes	1	Yes	I	Rheumatism and acute endocarditis just before onset of chorea
146	171	Litten, 1886	22 M	I	Yes	*	4	L	*Chorea, acute rheumatism and endocarditis at the same time
147	172	Litten, 1886	24 S	II		*	3	L	*Chorea, acute rheumatism and endocarditis at the same time
148	173	Litten, 1886	20 M	I	Yes	1	A p in third month	L	
149	174	Litten, 1886		I	Yes	Yes	P p	L	Rheumatism just before onset of chorea, which was complicated by acute endocarditis
150	175	Litten, 1886	20	I		3	P p	L	
151	176	Litten, 1886	23 M	III		3	P p	L	
152	177	Litten, 1886		I		9	Until death	D	Death one day post partum, autopsy serous effusion over the brain
153	178	Litten, 1886	23 S	I		*	Ycs	D	*Onset of chorea prior to third month, autopsy acute endocarditis, general septicemia and purulent effusion in the joints

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151	179	Litten, 1886	17	S	I	Yes	Yes	Yes	2	Until death	Died undelivered in fourth month	D	D	Autopsy recent endocarditis
155	180	Guinon, 1886	19	S	I	Yes	Yes	Yes	2	Until death	Died undelivered in fourth month	D	D	Autopsy recent endocarditis, pneumonia, "absolute integrity of the central nervous system"
156a	181	Schuhl, 1886		M	I	Yes	No	No	3	A p in fifth month	Spontaneous premature labor at term	L	L	Onset of chorea after violent emotion, albuminuria
b	182	Schuhl, 1886	20	M	II	Yes	No	No	4	A p in seventh month	Spontaneous labor at term	L	L	
157a	183	Schweiger, 1886	25	M	I	Yes	Yes	Yes	2	P p	Spontaneous labor in fourth month	L	D	
b	184	Schweiger, 1886	25	M	II	Yes	Yes	Yes	2	P p	Spontaneous labor in fourth month	L	D	
158	185	Koch, 1887	27	M	I	Yes	Yes	Yes	2	P p	Spontaneous labor in fourth month	L	D	
159	186	Koch, 1887	19			Yes	Yes	Yes	6	P p *	Spontaneous premature labor	L	D	*Chorea ceased immediately post partum
160	187	Talent, 1887	17	S	I	Yes	Yes	No	6	P p	Induced premature labor in seventh month	L	L	
161	188	Kemper, 1887	23	M	II		Yes		4	Until death	Died undelivered at term	D	D	Fright preceded attack, fever
162	189	Volquardsen, 1887	21	M	I				5	A p	Spontaneous labor at term	L	L	
163	190	Wasseige, 1887	23	M	I				7	Until death	Accouchement forcé	D	D	Fright preceded attack, death a few hours post partum
164	191	Mackenzie, 1887 (Treharne)	19	S	I	No	Yes	Yes	5	1 month p p	Spontaneous labor in sixth month	L	D	Fright preceded attack, abortion two weeks after onset of chorea
165	192	Mackenzie, 1887 (Dobie)	20	M	I	Yes	Yes	No	4	1 month p p	Spontaneous abortion in sixth month	L	D	Puerperal mania in puerperium with recovery
166	193	Mackenzie, 1887 (Pearce)	26	M	II	Yes						L		
167	194	Mackenzie, 1887 (Thursfield)	24	M	I	Yes	Yes	No	2	Until death	Induced premature labor in eighth month	D	D	
168	195	Mackenzie, 1887 (Bentham)	23		II	No	Yes	No		A p *	Spontaneous labor at term	L		*Chorea lasted eight weeks
169	196	Mackenzie, 1887 (Handford)	19			Yes	Yes	Yes				L		

170a	197	Mackenzie, 1887 (Davis)	23	M	I	Yes	No	No	1	A p in seventh month	Spontaneous labor at term	L	L	Worry before onset of chorea
b	198	Mackenzie, 1887 (Davis)		M	II	Yes	No	No			Spontaneous labor at term	L		
171	199	Lehmann, 1887	23	S	I	No	No	No	7	A p *	Spontaneous labor at term	L	L	*Chorea lasted two weeks during preg nancy, but relapsed in the second month, post partum and lasted four months
172	200	Lehmann, 1887	30	M	VI	No	No	No	5	Until death	Died undelivered in seventh month	D	D	Autopsy negative
173	201	Lehmann, 1887	21	M	I		Yes		5	Until death	Spontaneous labor	D	D	Autopsy bronchial pneumonia and myocarditis
174	202	Thursfield, 1887	20	M	III	Yes	No	No	?	Until death	Induced abortion in fifth month	D	D	Death on eleventh day post partum, marked albuminuria
175	203	Dodge, 1888	23	M	III	No	No	No	6	In second month p p	Spontaneous labor at term	L	L	Chorea complicated by epilepsy
176	204	Hirst, 1888	18	M	I		No	No	3	A p in ninth month	Induced premature labor*	L	L	*Labor induced for puerperal mania
177	205	Hirst, 1865	19		I	Yes	No	No	1	15 days p p	Spontaneous labor at term	L	L	
178	206	Tait, 1888	21	S		Yes	Yes	No	2	P p	Induced premature labor in eighth month	L	D	
179	207	Goodell, 1888										L		
180	208	Hocquet 1888	25			Yes			3	A p in eighth month		L	L	Chorea complicated by hysteria
181	209	Hocquet, 1888	18		I	Yes	No	No	3	P p	Spontaneous labor at term	L	L	
182	210	Walker, 1888	20						*					*Onset of chorea before fourth month
183	211	No name, 1888								A p		L		Recovery followed application of iodine to cervix
184	212	Benedict, 1888	20	M	I	Yes			3	A p in fifth month		L		
185	213	Marshall, 1888	18	S	I	Yes			*	P p	Spontaneous labor at term	L	L	*Patient had chorea before preg nancy occurred
186a	214	Marshall, 1888	20	M	I	No			*	*	Spontaneous labor at term	L	L	*Chorea continued post partum
b	215	Marshall, 1888	22	M	II	Yes			*	*	Spontaneous labor at term	L	D	*Chorea had persisted since first preg nancy, fetal death due to breech presentation
c	216	Marshall, 1888	23	M	III	Yes			*	*	Spontaneous labor at term	L	L	*Chorea continuously since first preg nancy, and persisted post partum
187a	217	Sherman, 1888		M	I					P p	Spontaneous labor at term	L	L	
b	218	Sherman, 1888		M	II	Yes				P p	Spontaneous labor at term	L	L	
188	219	Handfield Jones, 1889	25	M	I	No	No	No	4	3 weeks p p	Induced abortion in sixth month	L	D	Fright preceded attack, acute mania
189	220	Handfield Jones, 1889	19	M	I		No	No	1	A p in fourth month	Spontaneous labor at term	L	L	
190	221	Charpentier, 1889	19		I				3	A p in eighth month	Spontaneous labor at term	L	L	
191	222	Charpentier, 1889	20		I	Yes			5	A p in seventh month	Spontaneous labor at term	L	L	

2037	239	Pantzer, 1890	M	III	No	Yes	7	2 months p p	Induced premature labor in eighth month	L	First two pregnancies free from chorea
b	240	Pantzer, 1890	M	IV	Yes	Yes	9		Spontaneous labor at term	L	
c	241	Pantzer, 1890	26	V	Yes	Yes	?	9 days p p		L	
204a	242	Bonnaud, 1890					No	3 1 or 2 months p p	Spontaneous labor at term	L	
b	243	Bonnaud, 1890		*	Yes	No	No	3 1 or 2 months p p	Spontaneous labor at term	L	*Multipara
c	244	Bonnaud, 1890		*	Yes	No	No	3 1 or 2 months p p	Spontaneous labor at term	L	*Multipara
205a	245	Hubert, 1890		I					Spontaneous labor at term	L	Chorea ceased following dilatation of the cervix
b	246	Hubert, 1890		II	Yes			A p	Spontaneous labor at term	L	*Chorea present when pregnancy began, albuminuria
206	247	Hicks, 1891	S	I	Yes	?	?	P p	Spontaneous labor at term	L	*Chorea present when pregnancy began, patient was epileptic
207	248	McCann, 1891	M	I	Yes	Yes	?	3 days p p	Spontaneous labor at term	L	First pregnancy normal
208	249	McCann, 1891	M	II	No	No	2	6 days p p	Induced premature labor in eighth month	L	
209a	250	McCann, 1891	M	I	Yes	No	5	P p	Spontaneous labor at term	L	
b	251	McCann, 1891	M	II	Yes	No	?	5 months p p	Spontaneous labor at term	L	
210	252	McCann, 1891 (Grigg)	M	I	Yes	Yes	4	P p	Spontaneous labor at term	L	No albuminuria
211	253	McCann, 1891 (Hooper)	S	I	?	?	?	P p	Spontaneous labor at term	L	No remarks
212	254	Cameron, 1891	M	III			?		Spontaneous labor at term	L	No albuminuria
213	255	Hensoldt, 1891	15	I	Yes	Yes	2	P p	Spontaneous labor at term	L	
214	256	Hensoldt, 1891	26	I			Yes	*	Spontaneous labor at term	L	*Chorea persisted post partum
215	257	Riehe, 1891	25	VI	No	No	2	4 days p p	Spontaneous premature labor in seventh month	L	Fright preceded attack, baby lived only fifteen days
216	258	Riehe, 1891	23	I	Yes	Yes	?		Spontaneous labor at term	L	
217	259	Riehe, 1891	22	I	No	No	?	P p	Spontaneous labor at term	L	
218a	260	Riehe, 1891	21	I	Yes	Yes	1	A p in fifth month	Spontaneous labor at term	L	
b	261	Riehe, 1891	24	II	Yes	Yes	1	A p in fifth month	Spontaneous labor at term	L	
219a	262	Riehe, 1891	M	I	No	No	2	8 days p p	Spontaneous labor at term	L	
b	263	Riehe, 1891	M	II	Yes	No	2	P p *	Spontaneous labor at term	L	*Chorea ceased immediately after an attack of post partum eclampsia
c	264	Riehe, 1891	M	III	Yes	No	2	8 days p p	Spontaneous abortion in fourth month	L	
d	265	Riehe, 1891	M	IV	Yes	No	2	8 days p p	Spontaneous abortion in fourth month	L	

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			27	M	V	Yes	No	No	5	3 days	Spontaneous pre mature labor in eighth month	L	L	No albuminuria
220	266	Riche, 1891	26	S	I	No	No	?	9	Few days p p	Spontaneous labor at term	L	L	Autopsy negative, but patient evidently died of puerperal infection.
221	268	Turner, 1892	19	M		No	No	?	2	Until death	Spontaneous pre mature labor in seventh month	L	D	*Pregnancy antedated marriage, urine normal
222	269	Marx, 1892	23	*	I	No	No		1	2 weeks p p	Spontaneous labor at term*	L	D	*Cranotomy, urine normal
223	270	Marx, 1892	20		I	Yes	Yes		3	10 days p p	Spontaneous labor at term*	L	D	Autopsy negative, albuminuria
224	271	Fris, 1892	24			Yes		?	3	Until death	Died undelivered in fifth month	D	D	
225	272	Fris, 1892	27	M	I				5	*	Spontaneous labor at term	L	L	*Chorea persisted post partum, as long as patient was under observation
226	273	Schwarze, 1892	20		I				6	P p	Spontaneous pre mature labor	L	L	
227	274	Schwarze, 1892	22		I	No	No	Yes	6	Until death	Induced premature labor in seventh month	D	D	Autopsy negative except for acute endocarditis
228	275	Walls, 1892	19	M	I	No	No		*	P p	Spontaneous pre mature labor	L	L	*Chorea present when pregnancy began
229	276	Lloyd, 1893	22	S	I	Yes	Yes	No	*	*	Spontaneous pre mature labor	L	L	*Chorea present when pregnancy began
230	277	Lloyd, 1893	39	M	V	No	No		*	*	Induced premature labor in seventh month	L	L	and was still present five years post partum
231	278	Hünermann, 1893	18		I		Yes	No	1		Spontaneous pre mature labor	L	L	
232	279	Fontenau, 1893	19		I	No			2	19 days p p	Spontaneous labor in third month	L	D	
233	280	Fontenau, 1893	19		I				5	18 days p p	Spontaneous pre mature labor	L	D	Chorea complicated by hysteria
234	281	Fontenau, 1893	19	S	I	No	No		5	10 days p p	Spontaneous labor at term	L	L	Emotional disturbance preceded the onset of the chorea
235	282	Fontenau, 1893	20	S	I	No	No		7	A p in fourth month	Spontaneous pre mature labor in eighth month	L	D	
236a	283	Fontenau, 1893	18		I	No	No		2					

b	284	Fontenau, 1893	19	II	Yes	?	1	A p in sixth month	L	
237a	285	Fontenau, 1893	17	I	Yes		3		L	Spontaneous pre mature labor in eighth month
b	286	Fontenau, 1893	18	II	Yes		3		L	Spontaneous labor at term
238a	287	Puech, 1893	23	I	No		1	1 month p p	L	Spontaneous labor at term
b	288	Puech, 1893	24	II	Yes		1	1 month p p	L	Spontaneous labor at term
239a	289	Brenton, 1893	19	I	Yes	Yes	1	A p	L	Spontaneous labor at term
b	290	Brenton, 1893	20	II	Yes	Yes	7	P p	L	Spontaneous labor at term
240	291	Leberson, 1894	23	M	I				L	Spontaneous labor at term
241	292	Davis, 1894	21	M	I	No	3	Until death	D	Induced abortion in third month
242	293	Beulque 1894	24	M	II		6	P p	L	Spontaneous labor at term
243	294	Beulque, 1894	23	I	No	No	3	10 days p p	L	Spontaneous pre mature labor
244	295	Beulque, 1894	20	I			4	3 days p p	L	Spontaneous pre mature labor
245	296	Hochstetter, 1894	18	I			4	P p	L	Spontaneous labor at term
246	297	Osler, 1894	20	M	I	Yes				
247	298	Osler, 1894	22	M	Yes		*			
248	299	Osler, 1894	21	M	Yes		4			
249	300	Osler, 1894	30	M	Yes		7	*		
250	301	Buist, 1895	21	M	No	No			D	Spontaneous labor at term
251a	302	Buist, 1895 (Croom)	25	M	No	No	3		L	Spontaneous abortion in fifth month
b	303	Buist, 1895 (Croom)	26	M	Yes	No	3		L	Spontaneous pre mature labor in seventh month
c	304	Buist, 1895 (Croom)	27	M	Yes	No	1	P p	L	Spontaneous labor at term
d	305	Buist, 1895 (Croom)	29	M	Yes	No	1	P p	L	Spontaneous pre mature labor in seventh month
e	306	Buist, 1895 (Croom)		M	Yes	No		P p	L	Spontaneous abortion in third month
252a	307	Buist, 1895 (Afleck)	20	M	I	Yes		A p	L	
b	308	Buist, 1895 (Afleck)		M	II	Yes			L	
c	309	Buist, 1895 (Afleck)	24	M	III	Yes		A p	L	
253	310	Buist, 1895 (Folkm)	19	M	I	No	5	A p *	L	
254	311	Buist, 1895 (Folkm)		III	No			A p *	L	
255	312	Buist, 1895 (Still)	26	M	II	No	6	3 months p p	L	Spontaneous labor at term
256	313	Arai, 1895	24	M	I		5	P p	L	Induced abortion in fifth month

*Early in pregnancy

*Chorea was still present two months post partum

*Chorea attributed to dyspareunia, ceased after hymen was incised
 *Chorea ceased after removal of urethral caruncle
 First pregnancy normal, no albuminuria

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257	314	Lantos, 1895	24	M	IV	Yes			2	P p	Induced abortion in third month	L	D	No chorea or hyperemesis in first three pregnancies
258a	315	Haultain, 1895			I							L		
b	316	Haultain, 1895			II	Yes			1	P p	Spontaneous labor at term	L		
259a	317	Crouch, 1895		M	I	No			8	Few days p p	Spontaneous labor at term	L		
b	318	Crouch, 1895		M	II	Yes				P p	Spontaneous labor at term	L		
c	319	Crouch, 1895		M	III	Yes				P p	Spontaneous labor at term	L		
d	320	Crouch, 1895	32	M	IV	Yes				P p	Spontaneous labor at term	L	L	
e	321	Crouch, 1895	35	M	V	Yes				15 days p p	Spontaneous labor at term	L		
260	322	von Bechterew, 1896										D		
261	323	Kroner, 1896	20		I	No	No	No	4	2 weeks p p	Induced abortion in fifth month	L	D	
262	324	Tinley, 1896	28	S	I	Yes	Yes	No	*	Until death	Induced abortion in fifth month	D	D	*Chorea began before third month, death on second day post partum
263	325	Catherson, 1896	20	M	II	Yes			*	Until death	Spontaneous labor at term	D		*Chorea began on second day post partum, high fever, death in forty-eight hours
264	326	Flynn, 1896		M		Yes	Yes	?	3	A p in eighth month	Spontaneous labor at term	L	L	No albuminuria
265	327	Flynn, 1896	21	M	I	No	Yes	?	2	A p in fifth month	Spontaneous premature labor in eighth month	L	D	Baby stillborn
266	328	Milligan, 1896	26	M	I			Yes	2	Until death	Spontaneous labor at term	D		Death on sixth day post partum, autopsy endocarditis, embolism of the middle cerebral artery and rupture of small branch of same vessel
267a	329	Cameron, 1896	27	M	III	Yes	Yes		*	P p	Spontaneous labor at term	L	L	*Chorea began before sixth month
b	330	Cameron, 1896	30	M	IV	Yes	Yes		7	P p	Spontaneous labor at term	L	L	

268	331	Festenber, 1897	26	M	III	No	No	2	4 days p p		L	D	First two pregnancies normal, no albuminuria, acute mania complicating the chorea
269	332	Collier, 1897	21	M	II	Yes	No	*	P p		L	D	*Chorea for two months before conception, fright preceded attack, improvement immediately after abortion
270	333	Dakin, 1897	22	M	II	No	No		Until death		D	D	First pregnancy normal, attempt to induce abortion failed, chloroform, autopsy cloudy swelling of viscera
271	334	Dakin, 1897	23	M	I	Yes	Yes	4	Until death		D	D	Attack lasted four days, chloroform, autopsy, cloudy swelling of the viscera
272	335	Dakin, 1897	18	S	I	No	Yes	?	P p *		L	D	*Chorea still present slightly one month post partum, mania, no albuminuria
273	336	Dakin, 1897	23	M	I		?	6	2 months p p		L	L	Chorea complicated by mania
274	337	Dakin, 1897	23	S	I	Yes	Yes	6	2 weeks p p		L	D	Chorea complicated by mania
275	338	Dakin, 1897	23	M	V	No	No	2					
276	339	Dakin, 1897	19	M	I	Yes	?	*	A p		L		*Chorea began before third month and lasted one month
277	340	Velde and Volkmann, 1898	21		I			7	P p		L	L	Albuminuria
278a	341	Velde and Volkmann, 1898	21		I	Yes		*			L		*Attack began in third trimester of pregnancy
b	342	Velde and Volkmann, 1898	23		II	Yes		2	P p on seventh day		L	L	Chorea worse just before delivery
279	343	Ashworth, 1898	27	M		No	No	7	Until death		D	L	No albuminuria, no fever, anemia, death four and a half hours post partum
280	344	Delage, 1898	19		I	Yes	Yes	?	A p in eighth month		L	L	Fright preceded attack
281	345	Delage, 1898	21	M	I	Yes		4	A p in seventh month		L	L	Emotional disturbance preceded attack, second pregnancy normal
282	346	Delage, 1898	27	M	I	Yes	No	1	P p *		L	L	*Chorea continued post partum, as long as patient was under observation
283a	347	Delage, 1898	20		I	Yes	Yes	1	P p		L	L	
b	348	Delage, 1898	21		II	Yes	Yes	1	P p		L	L	
c	349	Delage, 1898	24		III	Yes	Yes	1	2 days p p		L	L	No albuminuria
284	350	Delage, 1898 (Duchemin)	18		I	Yes		3			L	L	
285	351	Delage, 1898 (Bernheim)	20		I			7			L	L	
286	352	Delage, 1898 (Bernheim)	19		I	Yes					L	L	
287	353	Delage, 1898 (Rontey)	21		I	Yes		4			L	L	
288	354	Delage, 1898 (Thoyer)	27		I						L	L	
289	355	Hartwig, 1898	19		Yes		No	6	A p in eighth month		L		

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200	356	Schroek, 1898	23		II				8	2 weeks p p	Spontaneous premature labor in seventh month	L	D	First pregnancy normal
201	357	Heymann, 1899									Induced premature labor in seventh month	L	D	
202	358	Master, 1899	17	M	I	No	No	No	1	A p in third month	Spontaneous labor at term	L	L	Albuminuria, chorea complicated by mania
203	359	Gilles de la Tourette, 1899	17		II									
204	360	Gilles de la Tourette, 1899			II	Yes	Yes	2						
205	361	Pinna, 1899	20		I	Yes		5	10 days p p		Induced abortion in fifth month	L	D	
206	362	Pinna, 1899	23	M	I		Yes	1	Until death		Induced abortion in fourth month	D	D	Autopsy negative except for vegetations on heart valves
207	363	Gentn, 1899			I			7	A p in ninth month		Spontaneous labor at term	L	D	Two subsequent pregnancies normal
208	364	Gentn, 1899	22		I			1	A p		Spontaneous labor at term	L	L	
209	365	Gentn, 1899	21		I	Yes		5	A p		Spontaneous labor at term	L		Emotional disturbance preceded attack, fetus had spina bifida and hydrocephalus
300	366	Gentn, 1899	17		II	Yes			A p		Spontaneous labor at term	L	L	No albuminuria
301	367	Gentn, 1899	20		I	Yes		1	A p in second month		Spontaneous labor at term	L	L	
302	368	Gentn, 1899	19		I	Yes		*			Spontaneous labor at term	L	L	*Patient had had chorea continuously since her twelfth year
303	369	Gentn, 1899	17		I	Yes		1			Spontaneous labor at term	L		
304	370	Gentn, 1899			I	Yes	Yes					L		Second pregnancy normal
305	371	Gentn, 1899			I							L		Fetus had spina bifida, clubfoot and hydrocephalus, second pregnancy normal
306	372	Gentn, 1899	18	III		Yes	Yes		A p			L	D	Baby died of pemphigus on ninth day
307	373	Gentn, 1899	18	II		Yes	Yes		A p		Spontaneous labor at term	L	L	First pregnancy normal

[illegible]

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329	401	Jolly, 1901							7	Until death	Spontaneous premature labor	D		Death a few days post partum
330	402	Hennig, 1901	25	M	II	No	No	No	6	P p	Spontaneous labor at term	L	D	First pregnancy normal
331	403	Routh, 1901		M	I	No	No	No	4	A p in sixth month	Induced abortion	L		
332	404	Routh, 1901 (Pollock)	20	S			No	No		P p		L	D	Patient kept under chloroform by relays of students, puerperal psychosis
333	405	Newell, 1901	19		I	Yes		?	2	A p in eighth month	Spontaneous labor at term	L		
334	406	Newell, 1901			I	Yes				P p		L		
335	407	Newell, 1901			I	Yes				P p		L		
336	408	Newell, 1901			I	Yes				P p		L		
337	409	Newell, 1901			I	Yes				P p		L		
338	410	Newell, 1901			I	Yes				P p		L		
339	411	Newell, 1901			I	Yes				P p		L		
340	412	Newell, 1901			I	Yes				P p		L		
341	413	Newell, 1901			I	Yes				P p		L		
342	414	Newell, 1901			I	Yes				P p		L		
343	415	Newell, 1901			I	Yes				P p		L		
344	416	Newell, 1901			I	Yes				P p		L		
345	417	Newell, 1901			III	No				P p		L		
346	418	Newell, 1901			II	Yes				P p		L		
347	419	Kruger, 1902	20		I	No	No		1	8 days p p	Induced premature labor in seventh month	L	D	First two pregnancies normal First pregnancy normal
348	420	Kruger, 1902	18		II				2	9 days p p	Induced abortion in third month	L	D	
349	421	Menzel, 1902	21	M	I		No	No	2	P p	Spontaneous labor at term	L	L	
350	422	Bumm, 1902	21		I				3	8 days p p	Vaginal hysterotomy	I	D	
351a	423	Jones, 1903	21	S					5		Spontaneous labor at term	L	D	Stillbirth, mania preceded onset of the chorea
b	424	Jones, 1903	23	S		Yes			6	*	Spontaneous premature labor	L		*Chorea persisting three months post partum, mania in this pregnancy also

352	425	Copeman, 1903	28	M	III	No	No	No	3	A p in fourth month	L	Tonsillitis preceded the attack, which cleared up following removal of uterine caruncle
353	426	Helher, 1903	23	M	II	No	Yes	?	3	6 weeks p p	L	Spontaneous labor at term
354	427	Hart, 1903	18	M	II	No	No	No	2	3 weeks p p	L	Induced abortion in second month
355	428	Hart, 1903	19	M	I	No	Yes	No	4	A p in sixth month	L	Fright preceded attack, some mental disturbance, first pregnancy normal
356	429	Wall and Andrews, 1903	21	M	I	No	Yes	No	6	6 weeks p p	L	
357	430	Wall and Andrews, 1903	20	M	II	Yes	No	No	3	A p in fourth month	L	Fright preceded attack
358	431	Wall and Andrews, 1903	19	M	I	Yes	Yes	No	4	A p in seventh month	L	
359	432	Wall and Andrews, 1903	22	M	III	Yes	No	No	5	A p in seventh month	L	
360	433	Wall and Andrews, 1903	23	M	I	Yes	Yes	Yes	6	10 days p p	L	First two pregnancies normal
361	434	Wall and Andrews, 1903	23	M	III	No	No	No	3	A p in fifth month	L	Fright preceded attack
362	435	Wall and Andrews, 1903	24	M	I	Yes	No	No	2	A p in third month	L	
363	436	Wall and Andrews, 1903	22	M	I	Yes	No	No	2	No	L	
364	437	Wall and Andrews, 1903	20	M	I	Yes	No	No	5	A p in fifth month	L	Fright preceded attack, slight albuminuria
365	438	Wall and Andrews, 1903	18	S	I	No	No	Yes	4	No	L	Fright preceded the attack
366	439	Wall and Andrews, 1903	33	M	VII	No	No	No	6	No	L	Fright preceded the attack, first pregnancy normal
367	440	Wall and Andrews, 1903	22	M	II	Yes	No	Yes	5	No	L	
368	441	Wall and Andrews, 1903	27	M	I	Yes	No	Yes	*	No	L	*Onset of chorea preceded the pregnancy by one month, improvement following the abortion, but the chorea continued, chorea complicated by acute rheumatism
369	442	Wall and Andrews, 1903	20	M	I	Yes	Yes	No		Induced abortion	D	
370	443	Wall and Andrews, 1903	19	S	I	No	No	No	6		L	
371	444	Wall and Andrews, 1903	21	S	I	Yes	No	Yes	2		L	
372	445	Wall and Andrews, 1903	22	M	I	Yes	No	No	6	A p in seventh month	L	
373	446	Wall and Andrews, 1903	22	M	II	Yes	No	No	6		L	
374	447	Wall and Andrews, 1903	26	M	III	Yes	No	No	8		L	
375	448	Wall and Andrews, 1903	19	S	I	Yes	Yes	No	5		L	Patient much worried before attack of chorea
376	449	Wall and Andrews, 1903	25	M	II	No	Yes	Yes	4	A p in seventh month	L	Emotional disturbance preceded the onset of the chorea
377	450	Wall and Andrews, 1903	18	M	I	No	No	No	3		L	Patient was syphilitic
378	451	Wall and Andrews, 1903	21	M	I	No	No	No	3		L	Stillbirth, patient much worried before the attack of chorea
379	452	Wall and Andrews, 1903	22	S	I	Yes	No	No	7	7 weeks p p	D	
380	453	Wall and Andrews, 1903	23	M	III	No	Yes	Yes	2	Spontaneous premature labor in seventh month	D	Spontaneous rupture of ectopic pregnancy

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For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea	Time of Recovery from Chorea	Date of the Pregnancy	Result for Mother	Result for Child	Comment
381	454	Wall and Andrews, 1903 21	21	M	II	Yes	No	Yes	5	1 month p p	Spontaneous pre mature labor in seventh month	L	L	First pregnancy normal
382	455	Wall and Andrews, 1903 22	22	M	II	Yes	No	No	4		Spontaneous labor at term	L	L	
383	456	Wall and Andrews, 1903 22	22	M	I	Yes	No	No	7	4 weeks p p	Spontaneous labor at term	L	L	
384	457	Wall and Andrews, 1903 21	21	S	I	No	No	No	5	A p	Induced abortion	L	D	Patient worried before attack
385	458	Wall and Andrews, 1903 22	22	M	III	Yes	Yes	Yes		Until death	Induced abortion	D	D	Autopsy infected clot in uterus, endocarditis
386	459	Wall and Andrews, 1903 21	21	M	I	Yes	Yes	No		Until death	Induced abortion	D	D	Autopsy edema of lungs and endocarditis
387	460	Wall and Andrews, 1903 21	21	M	I	Yes	No	Yes	5	Until death	Induced abortion	D	D	Chorea treated with chloroform inhalations, first four pregnancies normal
388	461	Wall and Andrews, 1903 28	28	M	V	No	No	No	5	Until death	Induced abortion	D	D	First three pregnancies normal, patient worried before attack, mania
389	462	Wall and Andrews, 1903 23	23	M	IV	Yes	No	Yes	3	Until death	Died undelivered	D	D	Autopsy embolism in spleen, kidneys and left middle cerebral artery
390	463	Wall and Andrews, 1903 21	21	M	I	No	No	Yes	1	Until death	Induced abortion	D	D	
391a	464	Wall and Andrews, 1903 21	21	M	I	Yes	No	No	4		Spontaneous labor at term	L	L	Second pregnancy free from chorea
b	465	Wall and Andrews, 1903 26	26	M	III	Yes	No	No	8	5 weeks p p	Spontaneous labor at term	L	L	
392a	466	Wall and Andrews, 1903		M	I	Yes	No	Yes	3	4 weeks p p	Spontaneous pre mature labor in seventh month	L	L	
b	467	Wall and Andrews, 1903 25	25	M	II	Yes	No	No				L	L	
393a	468	Wall and Andrews, 1903 22	22	M	I	No	No	No				L	L	
b	469	Wall and Andrews, 1903 23	23	M	II	Yes	No	No				L	L	
c	470	Wall and Andrews, 1903 23	23	M	III	Yes	No	No	2			L	L	
394a	471	Wall and Andrews, 1903 15	15	M	I	No	Yes	Yes				L	L	
b	472	Wall and Andrews, 1903 29	29	M	XIII	Yes	Yes	Yes	4	3 weeks p p	Spontaneous pre mature labor in eighth month	L	L	Chorea in first and thirteenth pregnancies, seven pregnancies ended in miscarriage
395a	473	Rozenblum, 1903	24	M	II	Yes	No	No	1	P p	Induced abortion	L	D	First attack of chorea began two weeks after first labor
b	474	Rozenblum, 1903		M	III	Yes	No	No	1	P p	Spontaneous labor at term	L	L	

396	475	Duckworth, 1903	24	M	VIII		Yes	Yes	5	P p	Spontaneous labor	L	D	*Abortion began spontaneously, but was terminated surgically, fright preceded attack, mania, no albuminuria
397	476	Duckworth, 1903		M	*		Yes	No	5			L		*Mentally, fright preceded attack
398	477	Hirschl, 1903	20	S			No	No	8	9 days p p	Spontaneous pre mature labor in eighth month	L	L	Fright preceded attack, two attacks of mania
399	478	Dentler, 1903	32		III		Yes	Yes	8	Until death	Induced premature labor	D		Autopsy, recent endocarditis, purulent leptomeningitis, puerperal sepsis
400	479	Siemerling, 1904										D		
401	480	Siemerling, 1904										D		
402	481	Siemerling, 1904										D		
403	482	Siemerling, 1904				Yes			*			L		*Chorea for ten years before pregnancy, became worse during pregnancy and improved post partum
404	483	Vallois, 1904	26		I				6	1 week p p	Spontaneous pre mature labor in eighth month	L	L	Psychosis antedated the chorea and persisted post partum, albuminuria
405	484	Loquifer, 1904	25		III	No			4	A p in sixth month	Spontaneous labor at term	L	L	
406	485	Lequyer, 1904	26		I	No	No	No	5	P p	Spontaneous pre mature labor in eighth month	L	L	Fright preceded attack, puerperal psychosis, albuminuria
407	486	Shoemaker, 1904	17	S			Yes				Induced abortion in third month	D	D	Albuminuria
408	487	Seiple, 1904	24	M	I	No	No		3	Until death	Induced abortion in third month	L	D	*Acute rheumatism before beginning of pregnancy, albuminuria
409	488	Seiple, 1904	18	M	I	No	Yes	?	1	P p	Induced abortion in second month	D	D	Autopsy recent endocarditis, pyelitis, cystitis, metritis, bronchial pneumonia and hyperemia cerebri
410	489	Koritzkowski, 1904	18	M	I		Yes	Yes	3	Until death	Induced abortion in fifth month	L	D	
411	490	Koritzkowski, 1904	18	S	I				5	P p	Induced abortion in fifth month	L	D	
412a	491	Koritzkowski, 1904	26	M	II		No		9	4 days p p	Spontaneous labor at term	L	L	First pregnancy normal
b	492	Koritzkowski, 1904	28	M	III	Yes	No		5	4 days p p	Spontaneous labor at term	L	L	
c	493	Koritzkowski, 1904	30	M	IV	Yes	No	?	7	9 days p p	Spontaneous labor at term	L	L	
413	494	Koritzkowski, 1904	28							Until death		D		
414	495	(Abraham) Pelnitz, 1904					Yes					D		Autopsy congestion of brain, parenchymatous degeneration of various organs and endocarditis, see text
415	496	Frank, 1904	21	M	II		No	No	2	P p	Spontaneous labor at term	L	L	First pregnancy normal, albuminuria
416	497	Seiler, 1905	22	M	I	Yes			3	1 year p p	Spontaneous labor at term	L	L	
417	498	Seiler, 1905	26	M	I				5	Until death	Died undelivered in sixth month*	D	D	*Death following convulsions and coma twenty four hours after attempted induction of abortion under chloroform narcosis
418	499	Dixon, 1905	22	M	I		Yes	?	6	6 weeks p p	Spontaneous labor at term	L	L	Mania

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Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Date of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
419	500	Gould and Howell, 1905	19		I	No	No	?	8	A p in ninth month	Induced labor at term*	L	L	*Patient had eclampsia after recovery from chorea, and labor was induced for this indication, fright preceded attack
420	501	Gettkant, 1905	19		I	Yes	Yes	No	4	P p	Induced premature labor in eighth month	L	L	
421	502	Gettkant, 1905	18		I	Yes	No		*	P p	Spontaneous labor at term	L	L	*Onset of chorea early in pregnancy
422	503	Gettkant, 1905	19	M	II			?	2	P p	Induced premature labor in eighth month	L	L	First pregnancy normal
423a	504	Gettkant, 1905	19		I	No	No	No	3	P p	Induced abortion in sixth month	L	D	
b 505	505	Gettkant, 1905	20	M	II	Yes	No		7	P p	Induced premature labor in eighth month	L	D	
424	506	Kouwer, 1906			IV					P p	Spontaneous premature labor in eighth month	L		First three pregnancies normal, anemia
425	507	Shell, 1906		M	I	No	No	No	*	P p	Spontaneous labor in eighth month	L		*Onset of chorea in middle of pregnancy
426a	508	Shell, 1906	20	M	II	No	No	No	8	P p	Spontaneous labor at term	L	L	First pregnancy normal
b 509	509	Shell, 1906	23	M	III	Yes	No		5	Until death	Induced abortion at term	D	D	Maternal, chloroform inhalations to control chorea
427	510	Trench and Hicks, 1906	24	M	I	No	No	No	4	A p in seventh month	Spontaneous labor at term	L		Albuminuria
428	511	Trench and Hicks, 1906	19	S	I		Yes	Yes	7	A p in eighth month		L		Fright preceded attack
429	512	Trench and Hicks, 1906	20	M	I	Yes			1	Rapid recovery a p		L		
430	513	Trench and Hicks, 1906	20	M	I	No	No		1	Rapid recovery a p		L		
431	514	Trench and Hicks, 1906	22	M	III	No	No	No	1	A p in third month		L		First two pregnancies normal
432	515	Trench and Hicks, 1906	22	M	I	Yes		?	3	A p in fifth month		L		
433	516	Trench and Hicks, 1906	27	M	III	No	No	Yes	7	A p in eighth month		I		First two pregnancies normal

434	517	French and Hicks, 1906	21	S	No	No	No	4	A p in sixth month	L	
435	518	French and Hicks, 1906	23	M	III	Yes	No	4	Rapid recovery a p	L	First two pregnancies normal
436	519	French and Hicks, 1906	20	M	I	Yes	?	2	A p in fourth month	L	
437	520	French and Hicks, 1906	31	M	I	Yes	No	7	A p	L	
438	521	French and Hicks, 1906	21	M	I	Yes	Yes	6	P p	L	Spontaneous labor at term
439	522	French and Hicks, 1906	17	M	I	Yes	Yes	3	A p in sixth month	L	Spontaneous labor at term
440	523	French and Hicks, 1906	20	M	I	No	No	1	A p in third month	L	Fright preceded attack
441	524	French and Hicks, 1906	27	S		Yes	Yes	3	A p in sixth month	L	
442	525	French and Hicks, 1906	20	M	I	Yes	No	5	*	L	*Chorea was still present two months post partum
443	526	French and Hicks, 1906	21	S	I	No	No	2	A p in fifth month	L	
444	527	French and Hicks, 1906	30	M	II	Yes	No	7	2 weeks p p	L	First pregnancy normal, although chorea antedated it, *stillbirth
445	528	French and Hicks, 1906	22	M	III	No	No	4		L	Patient worried before attack, first two pregnancies normal
446	529	French and Hicks, 1906	30	M	II	Yes	Yes	2		L	First pregnancy normal, chorea complicated by acute rheumatism
447	530	French and Hicks, 1906	20	M	I	Yes	Yes	*	*		*Chorea present when pregnancy began and still present when patient passed from observation
448	531	French and Hicks, 1906	26	M	I	Yes	Yes	6		L	Spontaneous labor at term
449	532	French and Hicks, 1906	21	M	I	Yes	Yes	3	Until death	D	Spontaneous abortion in fourth month
450	533	French and Hicks, 1906	21	M	I	No	No	1	Until death	D	Autopsy recent endocarditis and par otitis, cultures from spleen, heart's blood and cerebrospinal fluid all sterile
451	534	French and Hicks, 1906	23	M	IV	No	No	5	Until death	D	Chloroform inhalations to control chorea, death on fifth day post partum, for autopsy see text
452a	535	French and Hicks, 1906		M	I	Yes	No	5	1 month p p	L	First three pregnancies normal, three weeks before death patient had a convulsion followed by coma and hemiplegia, autopsy recent endo carditis
b	536	French and Hicks, 1906	23	M	V	Yes	No	5	P p	L	Second, third and fourth pregnancies free from chorea
453a	537	French and Hicks, 1906		M	I	No	No	2	A p in third month	L	Spontaneous labor at term
b	538	French and Hicks, 1906	23	M	II	Yes	No	2	A p in third month	L	Spontaneous labor at term
454a	539	French and Hicks, 1906	16	M	I	Yes	Yes	*	1 month p p	L	Spontaneous pre mature labor in eighth month*
										D	*Chorea present before pregnancy began, stillbirth

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For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Disease of Cardiac	Month of Onset of Chorea§	Time of Recovery from Chorea#	Date of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
b 510		French and Hicks, 1906		M	II	Yes	Yes		2	1 month p p	Spontaneous abortion in fifth month	L	D	
c 511		French and Hicks, 1906	25	M	III	Yes	Yes		2	*	Spontaneous premature labor in seventh month	L	D	*Fetus died in sixth month, but pregnancy continued to seventh month with only slight improvement of chorea, which was still present when patient was discharged
555a	512	French and Hicks, 1906	*	M	I	No	No			P p	Spontaneous labor at term	L	L	*Patient under 20 years of age, fright preceded attack
b 513		French and Hicks, 1906	20	M	II	Yes	No		1	P p	Spontaneous labor at term	L	L	
450a	541	Martin, 1906	23	M	I	Yes	Yes		*	*	Spontaneous labor at term	L	L	*Chorea was present when pregnancy began and continued post partum
b 515		Martin, 1906		M	II	Yes	Yes		*	*	Spontaneous labor at term	L	L	*Chorea was present when pregnancy began and continued post partum
c 516		Martin, 1906		M	III	Yes	Yes	Yes	*	*	Induced abortion in sixth month	L	D	*Chorea was present when pregnancy began and continued post partum
d 547		Martin, 1906		M	IV	Yes	Yes	Yes	*	*	Spontaneous labor at term	L	L	*Chorea was present when pregnancy began and continued post partum
457	548	Poynton and Holmes 1906	16		I	Yes	Yes					L		
458	549	Templeton, 1906	23		II				2	P p	Pregnancy interrupted artificially*	L		*Month not given
459	550	Dubrandy, 1906	23	M	I				5	A p in seventh month	Spontaneous labor at term	L	L	Emotional disturbance before onset of chorea, second pregnancy normal
460	551	Mussellwhite, 1907	19	S	I				P p	P p	Spontaneous premature labor	L	D	Nausea for two weeks, no chorea in two subsequent pregnancies
461a	552	Foulkrod, 1907		M	I	Yes			P p	P p	Induced premature labor in eighth month	L	D	Eclampsia
b 553		Foulkrod, 1907		M	II	Yes				P p	Spontaneous abortion in fourth month	L	D	
c 554		Foulkrod, 1907		M	III	Yes				P p	Spontaneous abortion in third month	L	D	

d	555	Foulkrod, 1907	M	IV	Yes		P p	Spontaneous abortion in third month	L	D	
c	556	Foulkrod, 1907	25	M	V	Yes		Spontaneous labor	L	L	Rest, chloral and bromides
462	557	Frigyess, 1907	23		II	Yes	5	Until death			Autopsy congestion of brain and acute endocarditis
463	558	Goldberger, 1907	30		II		2	Until death			Fright preceded attack, two subsequent pregnancies normal
464	559	Meyer, 1907	36	M	IV	No	4	A p in fourth month	L	L	Emotional disturbance preceded onset of chorea
465	560	Meyer, 1907	25		I	No	7	2 weeks p p	L	L	Albuminuria
466	561	Meyer, 1907	20		I	Yes	*	A p	L	L	*Onset of chorea in middle third of pregnancy
467a	562	Meyer, 1907	20	M	I	Yes		1 day p p			*Onset of chorea in second half of pregnancy
b	563	Meyer, 1907	21	M	II	Yes	*				
468	564	Meyer, 1907 (Lloyd)	26		III	Yes	1	P p	L		Fright preceded attack, *labor term noted by accouchement force
469	565	Shaw, 1907	25		I	No	9	Until death	D	D	*Patient worried by forced marriage during pregnancy, death one month post partum from acute endocarditis
470	566	Shaw, 1907	18	*	I	No	*	2 weeks p p	D	D	
471	567	Shaw, 1907	30		I	No	5	A p in seventh month	L	L	Fright preceded attack
472	568	Shaw, 1907	25		I	Yes	3	A p in fifth month	L	D	Fetal death not due to chorea, stillbirth
473	569	Shaw, 1907	21	S	I		8	1 month p p	L	L	Mania, chorea became much worse after labor
474	570	Shaw, 1907	19		I	No	2	A p in sixth month	L	L	Emotional disturbance preceded attack
475	571	Shaw, 1907	21		I	Yes	6	A p in eighth month	L	L	
476	572	Shaw, 1907	27		I	Yes	7	3 weeks p p	L	L	
477	573	Shaw, 1907	23		I	No	6	20 days p p	L	D	Fetal death fourteen days post partum, probably not due to chorea
478	574	Shaw, 1907	33		III		5	A p in seventh month	L	L	
479a	575	Shaw, 1907	20		I	Yes		3 weeks p p	L	L	
b	576	Shaw, 1907	21		II		9	4 days p p	L	D	Baby had hydrocephalus
480a	577	Wallace, 1907	18		I	Yes	8	10 days p p	L	D	
b	578	Wallace, 1907	22		II	Yes	5	P p	L	L	
481	579	Gress, 1907	22	S	I	No					
482	580	Robertson, 1908	28	M	I	No	2	*	L	D	*Chorea still present eighteen months post partum

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Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea	Time of Recovery from Chorea	Date of the Pregnancy	Result for Mother	Result for Child	Comment
181	581	Robertson, 1908		M		No			1	P p	Induced abortion in second month	L	D	
181	582	Shaw, 1908	18	S	I	Yes			4	A p in seventh month	Spontaneous labor at term	L	L	
187	583	Shaw, 1908	21	*	I	No	No		1	10 days p p	Spontaneous abortion in fifth month	L	D	*Married during pregnancy, abortion attributed to pneumonia
186	584	Shaw, 1908	23	M	I	Yes			5	A p in eighth month	Spontaneous labor at term	L	L	
187	585	Quensel, 1908								A p	Accouchement forcé	L	D	
188	586	Quensel, 1908								A p	Accouchement forcé	L	D	
189	587	Quensel, 1908									Spontaneous abortion	D	D	
190	588	Quensel, 1908									Induced abortion	L	D	
191	589	Quensel, 1908							7					
192	590	Ifakkebonche and Gostenik, 1908	21		II					Until death	Induced abortion in fifth month	D	D	*Patient married during pregnancy, death forty-eight hours post partum, autopsy negative, bacteriologic examinations of blood and brain were negative
193	591	Birnbaum, 1910	18	*	I	No		No	2				D	First pregnancy normal, *chorea continued for eighteen months post partum
194	592	Viedenz, 1910	21	M	II	No			2	P p *	Spontaneous abortion	L	D	
195	593	Runge, 1910	25	M	V	No		Yes	5	1 week p p	Spontaneous labor at term	L	L	No chorea in other pregnancies
196	594	Runge, 1910	21	M	IV				3	3 months p p	Spontaneous premature labor in eighth month	L	D	
197	595	Runge, 1910	20	M	II	No			3	Until death	Died undelivered in fourth month	D	D	High fever, pulse rate, 160
198	596	Croft, 1910					*	Yes		Over 3 months p p	Spontaneous abortion at term	L	D	*Rheumatism complicated the chorea
199	597	Croft, 1910									Spontaneous labor at term	L	L	Severe attack associated with mental disturbance
200	598	Croft, 1910									Spontaneous labor at term	L	L	Severe attack associated with mental disturbance

501	599	Croft, 1910						Spontaneous labor at term	L	Severe attack associated with mental disturbance
502	600	Croft, 1910						Spontaneous labor at term	L	Severe attack associated with mental disturbance
503	601	Croft, 1910						Spontaneous labor at term	L	Severe attack associated with mental disturbance
504	602	Croft, 1910						Spontaneous labor at term	L	
505	603	Croft, 1910						Spontaneous labor at term	L	
506	604	Croft, 1910						Spontaneous labor at term	L	
507a	605	Croft, 1910	II				P p	Induced abortion in sixth month	L	
b	606	Croft, 1910	VI	Yes				Spontaneous labor at term	L	
508	607	Villupadierna, 1910	VI	No	Yes		Until death	Induced premature labor in eighth month	D	First five pregnancies normal, autopsy congestion of meninges and adhesions over motor area, old endocarditis
509	608	Diekman, 1911		Yes	No		Until death	Vaginal cesarean section	L	
510	609	Diekman, 1911		Yes					D	
511	610	Diekman, 1911		No	Yes		Until death	Vaginal cesarean section	D	
512	611	Diekman, 1911 (Courtant)					Until death	Spontaneous abortion in sixth month	D	Patient died ten days post partum, hypostatic pneumonia
513a	612	Diekman, 1911 (Hannes)	I						L	
b	613	Diekman, 1911 (Hannes)	II	Yes				Total vaginal extraction	D	*Chorea began in first trimester of pregnancy
c	614	Diekman, 1911 (Hannes)	III	Yes		*	Until death	Induced abortion in fifth month	L	First three pregnancies normal, acute articular rheumatism since third pregnancy
514	615	Randle, 1912	IV	No	Yes	4	2 weeks p p		L	Psychosis with the chorea
515	616	Nicolaier, 1912	II			5	P p	Spontaneous labor at term	L	
516	617	Chotzen, 1912						Spontaneous labor at term	L	
517	618	Chotzen, 1912						Spontaneous labor at term	L	
518	619	Chotzen, 1912						Pregnancy interrupted artificially*	D	*Month not given
519a	620	Chotzen, 1912					P p	Spontaneous labor at term	L	
b	621	Chotzen, 1912	*	Yes			P p	Induced interruption of pregnancy	L	*Multipara
520	622	Kramer, 1912			Yes		Until death	Pregnancy interrupted artificially*	D	*Month not given, autopsy endocarditis and myocarditis
521	623	Kramer, 1912		Yes			A p	Spontaneous labor at term	L	
522	624	Kramer, 1912					A p *	Spontaneous labor at term	L	*Attack lasted eight weeks

TABLE 1--1 *Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Chronic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians--Continued*

For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea	Time of Recovery from Chorea	Site of the Pregnancy	Result for Mother	Result for Child	Comment
523a	625	Kramer, 1912		M	*	Yes		Yes		Until death	Spontaneous interruption of pregnancy	L		* Multipara autopsy endocarditis and myocarditis
523b	626	Kramer, 1912		M	*	Yes		Yes		Until death	Induced interruption of pregnancy	L		* Multipara, autopsy endocarditis and myocarditis
525	629	Meumann, 1912	21		I	Yes	Yes	No		P p	Spontaneous labor at term	L	L	No albuminuria
526	630	Meumann, 1912	18	S	I	Yes	Yes	Yes		P p	Spontaneous labor at term	L	L	No albuminuria
527	631	Meumann, 1912	19	M	I				6	Until death	Induced premature labor	L	L	Tight preceded the attack, no albuminuria, first pregnancy normal
528	632	Meumann, 1912	23	M	I			?	*	P p	Induced abortion in sixth month	L	D	* Onset of chorea before sixth month, complicated by hysterical hemiparesis, no albuminuria
529	633	Meumann, 1912	20	S	II	No	No	No	S	P p	Induced labor at term	D	D	First two pregnancies normal, no albuminuria
530	634	Meumann, 1912	20		II				9	Until death	Induced abortion in sixth month	D	D	Albuminuria
531	635	Meumann, 1912	25	M	III			?	9	Until death	Induced premature labor in sixth month	L	D	No albuminuria
532	636	Meumann, 1912	20	S	I	Yes		No	5	Until death	Induced premature labor in fifth month	L	D	No albuminuria
533	637	Meumann, 1912	25	S	I	Yes		No	9	P p	Induced abortion in sixth month	D	D	* Early onset, no albuminuria, death on second day post partum, first two pregnancies normal
534	638	Meumann, 1912	22	M	III	No	No	?	*	Until death	Induced premature labor	L	D	Albuminuria
535a	639	Meumann, 1912	27		I	Yes	Yes		6	9 days p p	Induced abortion in sixth month	L	D	Third pregnancy free from chorea, albuminuria
535b	640	Meumann, 1912	28		II	Yes	Yes		6	P p	Spontaneous labor at term	L	L	
535c	641	Meumann, 1912	31		IV	Yes	Yes	?	6	P p				
536a	642	Meumann, 1912	21	M	I	No	No		3	A p in fifth				

b	643	Meumann, 1912	23	M	II	Yes	No	Yes	1	P p	Vaginal hysterotomy in fourth month	L	D	No albuminuria
537	644	Dobkevitch, 1913	25	M	II				2	1 day p p	Induced abortion in fourth month	D	D	Patient given 20 cc of blood serum from normal pregnant woman, first pregnancy normal
538	645	Dobkevitch, 1913 (Ballantine)	25	M	I	Yes			3	Until death	Died undelivered	D	D	Onset of chorea followed the extraction of a tooth
539	646	Potocki and Sauvage, 1913	20		I	No	No	Yes	2	Until death	Died undelivered in third month*	D	D	*Death three weeks after onset of chorea and four hours after attempted abortion, no albuminuria autopsy recent severe endocarditis
540	647	Frapont, 1913	29	M	I	No			5	3 days p p *	Spontaneous premature labor in ninth month	D	L	*Chorea improved at once after delivery, but mania and fever developed with no evidence of postpartum infection, no albuminuria, great anger preceding the onset of the attack
541	648	Frapont, 1913	25	M	II				5	12 days p p	Spontaneous labor at term	L	L	Irright preceded the attack, no albuminuria, first pregnancy normal
542a	649	Frapont, 1913	23	M	III	Yes			7	12 days p p	Spontaneous labor at term	L	L	First two pregnancies free from chorea
b	650	Frapont, 1913	25	M	IV	Yes			1	10 days p p	Spontaneous labor at term	L	L	
543	651	Hurtel		S				No	7	A p in eighth month		L		Treated with arsenamine, Wassermann reaction negative, no albuminuria
544	652	Wilson, 1913	23			No	No	No	5	Until death	Died undelivered in seventh month	D	D	Patient syphilitic, for autopsy see text
545	653	Hoff, 1913	26				Yes	?	3					
546	654	Hoff, 1913	23	M					2		Spontaneous premature labor in seventh month	L	D	
547	655	Hoff, 1913	24	M					7	P p	Induced abortion			
548	656	Muhlbaum, 1913	24	S		Yes	Yes	?	*	1 month p p	Spontaneous premature labor in eighth month	L	D	*Onset of chorea early in pregnancy
549a	657	Muhlbaum, 1913	21	M	I				6	8 weeks p p	Spontaneous premature labor in eighth month	L	D	
b	658	Muhlbaum, 1913	22	M	II	Yes	Yes	No	3	2 weeks p p	Induced abortion in third month	I	D	Psychosis
c	659	Muhlbaum, 1913		M	III	Yes			*	P p	Induced abortion	I	D	*Onset of chorea early in pregnancy
d	660	Muhlbaum, 1913	26	M	IV	Yes	Yes	Yes	1	Until death	Vaginal extraction of uterus	D	D	Autopsy recent endocarditis, parenchymatous nephritis
550	661	Sorbi, 1914	23	M	I	Yes		?	4	*	Spontaneous labor at term	L		*Chorea persisted in mild form
551*	662*	Shaw, 1914												*Twenty cases with recovery in each case, no other data
to 570 to 681														*Twenty eight cases with recovery in each case, no other data
571*	682*	Wall and Andrews, 1914												Chorea complicated by psychosis, first pregnancy ended with miscarriage
to 598 to 709														Albuminuria
599	710	Kolde, 1914	20	M	II	No	No	?	7	12 days p p	Spontaneous labor at term	I	L	
600	711	Ayers, 1915						No		Until death	Induced abortion	D	D	
601	712	Ayers, 1915	18			No	No	No		Until death	Induced abortion	D	D	
602	713	Ayers, 1915	23			Yes	Yes	Yes	1	2 weeks p p	Induced abortion in fourth month	L	D	

For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea	P p	Time of Recovery from Chorea	Fate of the Pregnancy	Result for Mother	Result for Child	Comment
603	714	Albrecht, 1915	20	I	I	Yes	?	No	2	A p In fifth month	P p	Spontaneous labor at term	T		Cure of chorea attributed to injections of blood serum of pregnant woman in first three pregnancies normal, but these retarded the attack of rheumatism
604	715	Albrecht, 1915	22	II	II	Yes	Yes	No	2	A p In fifth month	P p	Spontaneous labor at term	T		First three pregnancies normal, but these retarded the attack of rheumatism
605	716	Matthews, 1916	24	M	IV	Yes	Yes	Yes	1	P p		Induced abortion in second month	L	D	First three pregnancies normal, but these retarded the attack of rheumatism
606	717	Haneborg, 1916				Yes									First three pregnancies normal, but these retarded the attack of rheumatism
607	718	Vetlesen, 1916	21	M	II	No	No	No	4			Induced abortion in third month	L	D	First three pregnancies normal, but these retarded the attack of rheumatism
608	719	Flamma, 1917	21	M	I	No	No	No	*	10 days p p		Spontaneous abortion in third month	L	D	First three pregnancies normal, but these retarded the attack of rheumatism
609	720	Schuster, 1920	22	M	II	Yes	Yes	Yes	1	Until death		Spontaneous labor at term	L	D	First three pregnancies normal, but these retarded the attack of rheumatism
610	721	Royston, 1920	20	M	I	Yes	Yes	Yes	2	3 weeks p p		Curettage in second month	L	D	First three pregnancies normal, but these retarded the attack of rheumatism
611	722	Royston, 1920	20	M	I	No	Yes	Yes	2	5 weeks p p		Curettage in second month	L	D	First three pregnancies normal, but these retarded the attack of rheumatism
612	723	Royston, 1920	25	M	I	No	No	No	2	9 days p p		Spontaneous abortion in fourth month	L	D	First three pregnancies normal, but these retarded the attack of rheumatism
613	724	Royston, 1920	21	S	I	Yes	Yes	Yes	3	Until death		Induced abortion in fifth month	D	D	First three pregnancies normal, but these retarded the attack of rheumatism
614	725	Royston, 1920	25	M	IV	No	No	Yes	6	Until death		Accouchement forced in eighth month	D	D	First three pregnancies normal, but these retarded the attack of rheumatism

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For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea	Time of Recovery from Chorea	Date of the Pregnancy	Result for Mother	Result for Child	Comment
631a	717	Allard, 1921	18	I	I	Yes			1	2 months p p	Spontaneous abortion in sixth month	I	D	Marked albuminuria
b	718	Allard, 1921	20	II	Yes	Yes			1		Spontaneous premature labor	I	D	Marked albuminuria, placental
c	719	Allard, 1921	21	VI	Yes	Yes			1		Spontaneous abortion in fourth month	I	D	No albuminuria, third pregnancy ended in abortion, but there was no chorea
612a	750	Allard, 1921	21	I	Yes	Yes			1	P p	Spontaneous abortion in fifth month	I	D	
b	751	Allard, 1921	26	II	Yes	Yes			1	A p in seventh month	Spontaneous labor at term	I	D	
633a	752	Allard, 1921		I	Yes	Yes			*	P p	Induced abortion in third month	L	D	*Onset of chorea before third month
b	753	Allard, 1921		II	Yes	Yes				P p	Spontaneous abortion in sixth month	L	D	
c	754	Allard, 1921		V	Yes	Yes				P p	Induced abortion	I	D	No chorea in third or fourth pregnancies, but both babies died
d	755	Allard, 1921	20	VI	Yes	Yes					Spontaneous labor at term	I	L	*Chorea continued post partum
634a	756	Allard, 1921	20	I	Yes	Yes		Yes	1	P p	Spontaneous labor at term	L	L	
b	757	Allard, 1921	20	II	Yes	Yes		Yes	1		Spontaneous labor at term	I	L	Slight albuminuria
657* to 661	758*	Allard, 1921												*Twenty seven cases with recovery in each case no other data
662	757	Sieard, 1921	35						3	3 weeks p p	Induced abortion in third month at term	L	D	Delirium, fifteen months later patient developed parkinsonian syndrome
663	786	Meurer, 1921		VI	VI				8	P p	Spontaneous labor at term	L	I	No albuminuria
664a	787	Meurer, 1921 (DeSnoo)		I	I				3	A p in eighth month		L		
b	788	Meurer, 1921 (DeSnoo)	23	II	Yes	Yes			6	P p	Spontaneous labor at term	L	L	No albuminuria
665a	789	Meurer, 1921 (DeSnoo)		I	Yes	Yes			*	A p		L		*Chorea present before pregnancy began

b	c	790	Meurer, 1921 (DeSnoo)	25	II	Yes	I	P p	Spontaneous labor at term	L	Slight albuminuria, third pregnancy normal
666a	791	Meurer, 1921 (DeSnoo)	26	I	Yes	*	P p			L	
666b	792	Meurer, 1921 (DeSnoo)	32	II	Yes					L	*Onset of chorea in middle trimester of pregnancy, no albuminuria
667a	793	Meurer, 1921 (DeSnoo)	19	I	Yes	*	P p		Induced abortion in fourth month	I	*Onset of chorea early in pregnancy
667b	794	Meurer, 1921 (DeSnoo)		II	Yes	*	P p		Induced abortion in third month	L	*Onset of chorea early in pregnancy
668	795	Fruhnscholz, 1922	24	VI	Yes	Yes	0	12 days p p	Spontaneous abortion in sixth month	L	Fright preceded attack, slight albuminuria
669	796	McLean, 1922	22	M	Yes	?			Spontaneous labor at term	L	No albuminuria
670a	797	McLean, 1922		I	No	Yes			Induced premature labor in seventh month	L	Fright preceded attack
670b	798	McLean, 1922		II	Yes	Yes	*		Spontaneous abortion in third month	I	*Onset of chorea before third month, fright preceded attack
671	799	McLean, 1922	26	M	Yes	Yes	I	At p in ninth month	Spontaneous labor at term	I	
672	800	Ronsaville, 1922	35	M	No	No	9	2 weeks p p	Spontaneous labor at term	L	Slight albuminuria, casts in urine leukocytosis of 5,200, first pregnancy normal
673	801	Thunma, 1922	29	I	Yes	Yes	I		Spontaneous labor at term	L	
674	802	Marie, Boutin and Trctinkoff, 1923	21	M	No	Yes	I	Until death	Died undelivered in second month	D	1 or autopsy see text
675	803	Lucy, 1923	21	M	No	Yes	I	P p	Spontaneous labor at term	L	No albuminuria, leukocyte count, 5,600
676	804	Lucy, 1923	21	M	Yes	Yes	I		Spontaneous labor at term	L	No albuminuria, leukocyte count, 7,800
677	805	Iluc, 1923	27	M	No	No	I	At p in seventh month	Spontaneous labor at term	L	Choreiform movements intermittent, hysterix
678	806	Anderodias, 1924	15	I	No	No	7	2 weeks p p	Spontaneous premature labor	L	
679	807	Creutzfeldt, 1924	23	*	No	No	I	Until death	Spontaneous premature labor in eighth month	D	*Patient married during pregnancy, death three days post partum, for autopsy see text
680	808	Jacoby, 1925	18	S	Yes	Yes	2	2 weeks p p	Induced abortion in third month	L	No albuminuria
681	809	Jacoby, 1925	20	M	Yes	Yes	6	2 weeks p p	Spontaneous premature labor in seventh month	L	Attack followed emotional disturbance and blow on abdomen, no fever blood normal, blood pressure, 115 systolic
682	810	Jacoby, 1925		IV			6		Spontaneous premature labor in seventh month	L	Positive Wassermann reaction
683	811	Uregha and Elekcs, 1925	25	II	Yes	Yes	3	Until death	Abdominal cesar section in eighth month	D	1 ever and tachycardia, first pregnancy normal
	812								Induced abortion in third month	D	First attack of chorea six months after first labor, mania, for autopsy see text

TABLE I
Labdan Synopses of the Double Clinical and Pathologic Basis of Non-Hodgkin and Lymphoma (Hodgkin's) Compares, Contrasting
Labdan Synopses of the Double Clinical and Pathologic Basis of the Lymphoma and from a (Hodgkin's) Compares, Contrasting
in Lymphoma and Non-Hodgkin's Lymphoma, Collected from the Lymphoma and from a (Hodgkin's) Compares, Contrasting
in Lymphoma and Non-Hodgkin's Lymphoma, Collected from the Lymphoma and from a (Hodgkin's) Compares, Contrasting

Case	Age	Sex	Occupation	Onset	Duration	Location	Character	Course	Outcome	Remarks
1	25	M	Farmer	Sept 10	10 days	Left arm	Swelling, pain, redness	Spontaneous	Healed	First case of erysipelas
2	35	F	Housewife	Oct 5	14 days	Right leg	Swelling, pain, redness	Spontaneous	Healed	Second case of erysipelas
3	45	M	Blacksmith	Nov 15	21 days	Left arm	Swelling, pain, redness	Spontaneous	Healed	Third case of erysipelas
4	55	F	Teacher	Dec 1	18 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Fourth case of erysipelas
5	65	M	Farmer	Dec 15	25 days	Left leg	Swelling, pain, redness	Spontaneous	Healed	Fifth case of erysipelas
6	75	F	Housewife	Jan 1	30 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Sixth case of erysipelas
7	85	M	Blacksmith	Jan 15	35 days	Left arm	Swelling, pain, redness	Spontaneous	Healed	Seventh case of erysipelas
8	95	F	Teacher	Jan 30	40 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Eighth case of erysipelas
9	105	M	Farmer	Feb 5	45 days	Left leg	Swelling, pain, redness	Spontaneous	Healed	Ninth case of erysipelas
10	115	F	Housewife	Feb 15	50 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Tenth case of erysipelas
11	125	M	Blacksmith	Feb 25	55 days	Left arm	Swelling, pain, redness	Spontaneous	Healed	Eleventh case of erysipelas
12	135	F	Teacher	Mar 5	60 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Twelfth case of erysipelas
13	145	M	Farmer	Mar 15	65 days	Left leg	Swelling, pain, redness	Spontaneous	Healed	Thirteenth case of erysipelas
14	155	F	Housewife	Mar 25	70 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Fourteenth case of erysipelas
15	165	M	Blacksmith	Apr 5	75 days	Left arm	Swelling, pain, redness	Spontaneous	Healed	Fifteenth case of erysipelas
16	175	F	Teacher	Apr 15	80 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Sixteenth case of erysipelas
17	185	M	Farmer	Apr 25	85 days	Left leg	Swelling, pain, redness	Spontaneous	Healed	Seventeenth case of erysipelas
18	195	F	Housewife	May 5	90 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Eighteenth case of erysipelas
19	205	M	Blacksmith	May 15	95 days	Left arm	Swelling, pain, redness	Spontaneous	Healed	Nineteenth case of erysipelas
20	215	F	Teacher	May 25	100 days	Right arm	Swelling, pain, redness	Spontaneous	Healed	Twentieth case of erysipelas

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TABLE 1—Laboratory Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty One Chorea Pregnancies Occurring in Seven Hundred and Ninety-Six Persons, Collected from the Public Literature and from a Questionnaire Sent to Five Hundred and Fifty American Obstetricians—Continued

For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Current Disease	Month of Onset of Chorea	Time of Recovery from Chorea	Date of the Previous labor	Result for Mother	Result for Child	Comment
1717	54	Boyer, J. W., Washington, D. C.	22		II				I	P p	Spontaneous preterm labor	I	I	*Chorea ceased after tonsillectomy
1718	55	Carroll, W. T., Atlantic City, N. J.	21	M	I	No	No	No	I	A p *	Spontaneous labor at term	I	I	Severe attack of chorea controlled by intramuscular injections of meprobamate, death, due to pneumonia, on twelfth day of disease
1719	56	Dorsett, L., St. Louis	16	S	I	No	No	Yes	6	Until death	Delivered undelivered in sixth month	D	D	Patient had chorea from 7 to 11 years of age, aborted seven times, the full term children either were very delicate or died in infancy, no evidence of heart disease
1720a to 1720m	57* to 569	Lincoln, J., Montreal, Canada												
1721a	570	Findley, P., Omaha	20	M	I		No	No	1	P p	Spontaneous labor at term	L	L	
b	571	Findley, P., Omaha	12	M	II	Yes	No	No	1	P p	Abdominal hysterotomy in second month	L	D	
1722	572	Gillett, S., New York	22		I	Yes	No	No	5	A p in sixth month	Spontaneous labor at term	I	L	Patient had the symptoms of endocrine disturbance
1723	573	Goodman, S. J., Columbus, Ohio	21	M	I	No	No	No	3	10 weeks p p	Vaginal hysterotomy in third month	L	D	Unilateral chorea
1724	574	Hennrich, N. S., Chicago	21		I	No	No	No	1	P p	Vaginal hysterotomy	L	D	
1725	575	Hennrich, N. S., Chicago	25		IV	No	Yes	No	3	P p	Vaginal hysterotomy	L	D	Patient sterilized
1726	576	Kant, F. A. S., Cincinnati	23		I	Yes	Yes	Yes	5	A p in seventh month	Spontaneous labor at term	L	L	*Onset of chorea during labor, temperature, 101 F., pulse rate, 160, irrational, severe tonsillitis, and cervical adenitis in fifth month of pregnancy
1727	577	Kotz, J., Washington, D. C.	27	M	III	No	No	Yes	*	5 days p p				

†725	878	Iverson, H W, Wash ington, D C	19	M	I	No	No	?	1	1	Spontaneous pre mature labor in ninth month	L	L	Blood pressure, 120 systolic and 90 diastolic, Wassermann reaction negative, blood normal
†729	879	Litzenberg, J C, Minneapolis	25	M	I	No	No	?	1	1	Induced abortion in sixth month	L	D	Immediate improvement after the abortion
†730	880	Litzenberg, J C, Minneapolis				Yes				1				
†731	881	Longaker, D, Phila delphia	19	M	I	Yes	?	?	5	5	Spontaneous labor at term	L	D	
†732	882	Los Angeles General Hospital	15	I	I	Yes	Yes	?	2	2	Spontaneous labor at term	L	D	
†733	883	Los Angeles General Hospital	18	I	I	Yes	Yes	?	1	1	Spontaneous labor at term	L	L	
†734	884	Los Angeles General Hospital	17	V	V	Yes	Yes	?	*	*	Induced abortion	L	D	*Chorea ever since fourth labor patient sterilized
†735	885	Los Angeles General Hospital	16	I	I	Yes	No	No	3	3	1	L		
†736	886	Los Angeles General Hospital	19	I	I	No	No	No	5	5	Spontaneous labor at term	L	L	
†737	887	Lull, C B, Phila delphia	18	S	I	Yes	No	No	7	7	Until death	D	D	Temperature, 101 I
†738	888	Lull, O B, Phila delphia	21	M	I	Yes	No	No	1	1	Abdominal cesar ean section in ninth month	L	L	
†739a	889	Mann, B, Phila delphia	25	M	I	No	No	No	2	2	Spontaneous labor at term	L	D	*Attack lasted one month in all
†740	890	Mann, B, Phila delphia	28	M	II	Yes	No	No	3	3	Induced abortion	L	D	*Attack lasted five weeks in all
†741	891	Muller, W K, Phila delphia	18	I	I	Yes	?	?	*	*	Spontaneous labor at term	L	L	*Chorea present many years before pregnancy and continued post partum
†742	892	Mendenhall, A M, Indianapolis	26	M	I	Yes	No	No	3	3	Spontaneous labor in third month	L	D	*Attack lasted two weeks
†743	893	Newell, F S, Boston	16	I	I	Yes			5	5	Spontaneous labor at term	L	L	*Attack lasted three weeks
†744	894	Newell, F S, Boston	24	I	I	Yes	Yes	?	1	1				
†745	895	Nicholson, W R, Philadelphia	19	M	I	Yes	Yes	?	3	3	Spontaneous labor at term	L	L	
†746	896	Norris, C C, Phila delphia	20	M	II	Yes	No	No	3	3	Spontaneous labor at term	L	L	
†747	897	Norris, C C, Phila delphia	22	M	I	Yes	No	No	8	8	Spontaneous labor at term	L	L	
†748	898	Purum, J F, Cincinnati	21	I	I	No	No	No	1	1	Spontaneous labor at term	L	L	

TABLE 1.—A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Chorea Pregnantæ, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued

For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea	Time of Recovery from Chorea	Date of the Pregnancy	Result for Mother	Result for Child	Comment
1748	899	Pirrung, J. F., Cincinnati									Induced abortion in fourth month	L	D	
1749	900	Pirrung, J. F., Cincinnati									Spontaneous labor at term	L		
1750	901	Porter, W. D., Cincinnati									Spontaneous labor at term	L	L	
1751	902	Potter, I. W., Buffalo	30	M	I	No	No	No	4	P	Spontaneous labor at term	L	L	
1752	903	Potter, I. W., Buffalo	32	M	II	Yes	Yes	Yes	8	P	Spontaneous labor at term	L	L	
1753a	904	Potter, I. W., Buffalo	20	M	I	Yes	Yes	No	5		Spontaneous labor at term	L	L	
b	905	Potter, I. W., Buffalo	22	M	II	Yes	Yes	No	7		Spontaneous labor at term	L	L	
1754	906	Richards, J. L., Philadelphia	20	M	I	Yes	No	No	*	*	Spontaneous labor at term	L	L	*Chorea present at beginning of pregnancy and continued post partum
1755	907	Scott, A. J., Jr., Los Angeles	25		III	Yes	Yes	No	5	P	Spontaneous labor at term	L	L	Mild psychosis with the chorea
1756	908	Scott, W. A., Toronto, Canada	21	M		Yes		Yes	3	P	Induced abortion in fourth month	L	D	Patient developed mania and was sent to an asylum
1757	909	Scott, W. A., Toronto, Canada	22	M	III			No	2	P	Induced abortion	L	D	No chorea in two previous pregnancies
1758	910	Scott, W. A., Toronto, Canada	20	M	I	Yes	No	No	2	P	Induced abortion	L	D	
1759	911	Scott, W. A., Toronto, Canada	23	M	I	No	No		5	P	Spontaneous labor at term	L	L	
1760	912	Scott, W. A., Toronto, Canada	21	M	I	Yes		No	*	P	Spontaneous labor at term	L	L	*Chorea present at beginning of pregnancy
1761	913	Scott, W. A., Toronto, Canada	17	M	I	Yes	Yes	Yes	*	*	Spontaneous abortion in sixth month	L	D	*Chorea present at beginning of pregnancy and continued post partum
1762	914	Scott, W. A., Toronto, Canada	16	M		Yes		No	*	*				*Chorea present at beginning of pregnancy

Case No.	Name	Age	Sex	Marital Status	Yes	No	Chorea present at beginning of pregnancy, patient improved after the extraction of fourteen infected teeth
763	Scott, W A, Toronto, Canada	19	S	I	Yes	No	
761	Scott, W A, Toronto, Canada	16	S	Yes	Yes	No	Spontaneous labor at term
765	Scott, W A, Toronto, Canada	17	S	I	Yes	Yes	Vaginal hysterotomy
766	Scott, W A, Toronto, Canada	25	M	Yes	No	Yes	Spontaneous labor at term
767	Scott, W A, Toronto, Canada	21	S	I	Yes	No	Spontaneous labor at term
768	Scott, W A, Toronto, Canada	30	M	IV	Yes	7	Spontaneous labor at term
769	Scott, W A, Toronto, Canada	15	S	I	Yes	No	Spontaneous pre mature labor in seventh month
770	Scott, W A, Toronto, Canada		M	I	No	3	Induced abortion
771	Scott, W A, Toronto, Canada	20	S	Yes	?	No	Spontaneous labor at term
772	Scott, W A, Toronto, Canada	23	M				Spontaneous labor at term
773a	Scott, W A, Toronto, Canada	20	M	II	Yes		
773b	Scott, W A, Toronto, Canada	21	M	III	Yes	?	First pregnancy free from chorea
774	Spalding, A B, San Francisco	26	M	III	No	Yes	Two recurrences of the chorea during this pregnancy
775	Swift, J B, Jr., Boston	28	M	I	Yes	No	Spontaneous labor at term
776	Toombs, P W, Memphis, Tenn	22	I	I	No	No	Induced abortion in second month
777	van Sweringen, B, Fort Wayne, Ind	20	S	I	Yes	No	Spontaneous labor at term
778	Vaux, N W, Philadelphia	21	I	I	Yes	No	Abdominal cesarean section at term*
779	Vogt, E, Philadelphia	22	M	I	Yes	No	Spontaneous labor at term
780a	Vogt, E, Philadelphia	20	M	I	Yes	No	Induced abortion in sixth month
780b	Vogt, E, Philadelphia	21	M	II	Yes	No	Abdominal cesarean section*
781	Ward, G W, New York	21	M	I	Yes	?	
782	Williams, J W, Baltimore	20	M	III	Yes	No	Spontaneous labor at term
783	Williams, J W, Baltimore	17	S	I	Yes	No	Spontaneous labor at term
784	Williams, J W, Baltimore	18	M	V	No	No	Spontaneous pre mature labor

For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea	Time of Recovery from Chorea	Date of the Pregnancy	Result for Mother	Result for Child	Comment
1785	69	Williams, J W, Baltimore	23	M	IV	Yes	Yes	Yes	1					Albuminuria no chorea in previous pregnancies
1786	70	Williams, J W, Baltimore	16	S	I	No	No	No	*	P p	Spontaneous labor at term	L	L	*Onset of the chorea early in pregnancy, no albuminuria
1787	71	Williams, J W, Baltimore	18	S	I	No	No	?	3	A p in sixth month	Abdominal cesarean section in eighth month	L	D	*Operation for claustrula, patient died a few years later in an asylum
1788	72	Williams, J W, Baltimore	21	M	I	Yes	No	No	2	P p	Spontaneous labor at term	L	L	No albuminuria
1789	73	Williams, J W, Baltimore	19	M	I	No	No	Yes	6		Spontaneous labor at term	L	L	No albuminuria
1790	74	Williams, J W, Baltimore	20	M	I	Yes	No	No	7	P p	Induced premature labor	L	L	Albuminuria history of frequent tonsillitis, patient discharged with mental disturbance and died two years later in an asylum
1791	75	Williams, J W, Baltimore	19	M	I	Yes	No	No			Spontaneous labor at term	L	L	Blood pressure normal, no albuminuria, patient had chronically infected tonsils
1792	76	Williams, J W, Baltimore	19	M	I	No	No	No	3			L	L	No albuminuria, chemical analysis of blood negative, blood pressure normal, chronically infected tonsils
1793	77	Woodward, H L, Cincinnati	20	M	I	No	No	Yes	2	Until death*	Spontaneous abortion	D	D	*Very severe case, total duration three weeks
1794	78	Woodward, H L, Cincinnati	23	M	I	No	No	No	3	1 month p p	Induced abortion in third month	L	D	Patient's mother had chorea gravidarum
1795	79	Woodward, H L, Cincinnati	21	M	III	No	No	No	5					
1796	80	Woodward, H L, Cincinnati	22	M	I	Yes	No	No	*					*Chorea present at beginning of pregnancy
1797*	81	Willson and Preece	20	M	I	Yes	No	?	5	1 month p p	Induced abortion in sixth month	L	D	*Personal case for full report see text

† The numbers in this column marked † are cases taken from the questionnaire, and were previously unpublished a, b, c, etc, indicate successive chorea pregnancies in the same patient
‡ In this column S indicates single, M, married
§ In this column, and in others where they appear, the asterisks refer to the data marked with an asterisk in the column headed "Comment"
In this column, A p indicates ante partum, P p, post partum
¶ In this column, L indicates life, D, death

pitalization was from 90 to 112 until one week post partum, and then from 74 to 84 until discharge, except at the time of the fever noted, when the pulse reached 150. The urine was normal throughout. On September 4, the blood picture was hemoglobin, 70 per cent, red cells, 3,460,000, leukocytes, 9,600, polymorphonuclears, 80 per cent, lymphocytes, 18 per cent, eosinophils, 2 per cent.

HISTORY AND REVIEW OF THE LITERATURE

Felix Meyer gave a quotation in Latin from the works of Horstius, published in 1661, as a reference to what is possibly the first case of chorea gravidarum in the literature. The English translation would be as follows: "The following case, which occurred to the wife of a schoolmaster in childbirth, is, I think, of a peculiar nature. For more than twelve years since that event, for some reason or other, the whole of her left side is thus affected. When awake it is constantly in motion, which she cannot control by will. She is perpetually winking her eyes, her lips are continually opening and shutting, her arms keep jumping up, her fingers gesticulate, and her foot is never quiet. Yet all this occurs without feeling pain. But when she is asleep, everything is at rest." Levick stated that in Hecker's "Epidemics of the Middle Ages" there is a quotation from Burton's "Anatomy of Melancholy" that reads: "'Tis strange to hear how long they will dance, and in what manner, over stools, forms, tables even, great bellied women sometimes (and never hurt their children) will dance so long that they can stir neither hand nor foot." These references have been accepted by some as the earliest reported cases of chorea gravidarum, but the latter is obviously a reference to the outbreaks of religious mania associated with the cult of St. Vitus, the only relation of which to any type of chorea is that of having provided the common name of St. Vitus' dance, while the former is certainly open to considerable doubt as to the exact nature of the disease described.

In 1850, Sée reported 2 cases of his own and collected 12 from the literature. The earliest of these was attributed to Reidlin, but we have been unable to verify the reference. In 1862, Mosler tabulated 20 cases from the literature, the earliest of which was attributed to Ungen, but this reference could not be verified either. The case of Hand, however, reported in 1807, has been verified. These papers in French and German were followed by an important one read by Robert Barnes, in 1869, before the Obstetrical Society of London and published in its transactions. He reported 2 cases of his own and collected 46 others from various private sources and the literature. The interest aroused by these communications is indicated by the rapidly increasing number of case reports in the literature. The next milestone marking the progress of knowledge was the very able statistical paper by Buist, in 1894, before the Edinburgh Obstetrical Society. This author, after a most

exhaustive and meticulous survey of the literature, was able to tabulate a total of 256 cases occurring in 215 persons. These two papers and those of Wall and Andrews, French and Hicks, Shaw and Croft are undoubtedly the outstanding contributions to this subject in English. The German literature has been reviewed by Bamberg (1873), Gowers (1892) and Kioner (1896). By far the most important contribution in German, however, is the article by Pineles in 1913. This author collected 518 choreic pregnancies in 426 persons. The American literature contains little of importance except isolated case reports, with the exception of the recent papers by Royston and Campbell, and one by Newell, in 1901. In France and Germany interest is manifested by the large number of theses and inaugural dissertations on the subject, many containing elaborate compilations of case reports with, unfortunately, much duplication and copying. Vinay, in his "*Traité des maladies de la grossesse et des suites de couches*," published in 1894, devoted 10 pages to an able presentation of the subject.

Even a cursory examination of this literature will serve to demonstrate a quite remarkable lack of unanimity of opinion among those who have written on the subject, from the earliest articles until those of recent years as to the nature of chorea gravidarum. In general, however, these divergent views are subject to classification into two groups, as follows. First the belief that chorea in pregnancy represents a merely accidental association of the two and that the chorea is identical with the ordinary chorea of childhood. Second, the belief that it is entirely different from ordinary chorea, in other words, merely a choreiform condition either directly or indirectly dependent on pregnancy for its production. Some of the opinions that have been expressed on this subject may now be briefly reviewed.

A belief in the essential unity of Sydenham's chorea and chorea gravidarum was expressed as early as 1850 by See in the following opinion.¹ "Thus it may be supposed that pregnancy does not constitute the real cause and that it serves only as an intermediary of the actual causes of which it favors the production." In 1901, Laman, in a thesis that contains the best historical account in the literature, said "It is very certain that Sydenham's chorea, coming on during pregnancy or labor should not be confused with the ties or with hysterical chorea, for its clinical existence cannot be doubted." In 1903, Wall and Andrews said "In the first instance it has to be decided whether these cases are truly choreic, it seems necessary in most cases to answer in the affirmative. In fact, no distinguishing feature can be determined which points to any difference from the movements of Sydenham's chorea." In 1906, Poynton and Holmes made their well known "Contribution to the Pathology of Chorea," in which they expressed their belief in its rheumatic nature. They said "Chorea in pregnancy is probably a rheumatic chorea." They supported this statement with statistics showing the frequency with

¹ Direct quotations from the French and German literature are all translations.

which a history of rheumatism is obtained in these cases. In 1913, Pinard quoted Dieulafoy as follows: "Pregnancy generally makes the prognosis of chorea more grave, not that the chorea of pregnant women is a special form, but that, as Jaccoud has clearly shown, the gravid state associated with ordinary chorea aggravates its manifestations." In 1925, Urechia and Elekes stated that F. H. Lewy did not consider chorea in pregnancy as different from ordinary chorea, and they described the two together, giving the same pathology for each.

These views regarding chorea in pregnancy as identical with chorea in childhood find opposition as follows. In 1888, Hocquet expressed the opinion that "hysteria and chorea (in pregnancy) would appear to be two forms of the same malady." In 1891, Riche stated the position of this school of thought in the following words: "The special study which has been made of chorea of pregnancy is well justified. It is not an accidental complication of pregnancy, it is a disease, caused by pregnancy. This is proved by the facts that chorea of pregnancy appears at an age when simple chorea is exceedingly rare, that it lasts much longer than ordinary chorea, and that, finally, it ordinarily does not cease until the uterus has been emptied of its contents."

One rarely finds in the etiology of chorea in pregnancy the causes invoked by the majority of authors. One is then forced to admit that pregnancy itself can suffice to provoke the appearance of the chorea, and one can then explain this disease by saying that it is a reflex neurosis of which the point of departure may be the utero-ovarian plexus." In 1893, Duchateau described chorea in pregnancy as "choree autotoxique," and attributed its causation to an "eclampsie atténuee." In 1899, Giles de la Tourette identified it with the tics. In 1901, Newell stated: "Chorea deserves a special place in the pathology of pregnancy. It is not an accidental complication due to the recurrence of a previous infantile chorea, but in the majority of cases appears for the first time during pregnancy, that is, it is to a great extent produced by pregnancy. Pregnancy is not the only causative factor, but is the fundamental condition on which the other elements in the causation of chorea depend."

In 1908, Shaw, after an admirable study of the subject, reached the following conclusions:

- 1 "The chorea of pregnancy is due to a toxin which appears to be identical with, or closely to resemble, that of acute rheumatism."

- 2 "It affects human subjects under two circumstances, both of these being characterized by instability or irritability of the nervous system, namely, childhood and pregnancy."

- 3 "The cause of the instability or irritability of the nervous system in pregnancy, bringing it down to the level of childhood, is the toxemia of pregnancy."

These views are in substantial accord with those expressed in 1913 by Pinard, who said: "From the point of view of the prognosis of the so-called chorea of pregnancy I do not share medical opinion, nor do I share recent medical views concerning the pathology. Assuredly I believe, with many others, that that which is called chorea should be placed in the category of the neuroses. But I cannot admit that the choreic syndrome is the manifestation of an encephalitis or a meningo-encephalitis. Neither can the recently advanced view that chorea is of syphilitic origin be accepted by any informed physician. Being given the facts which I have observed of the reproductive function with chorea, I believe more than ever in an auto-intoxication manifesting itself by choreic symptoms in predisposed individuals. With Joffroy, I think it is an auto-intoxication, and an evolutionary disease (showing itself at the moment of the grasp of the individual by the species) and, with Latouche, I admit that pregnancy prolongs puberty." Finally, there are

the views recently expressed by the eminent neurologist, Sicard, that choreic manifestations in pregnancy are due to epidemic encephalitis. He said "Chorea of pregnancy sometimes allies itself to epidemic encephalitis. I have had occasion to report cases of the choreic syndrome developing during pregnancy, with choreic gesticulation and delirium without any of the classic signs of encephalitis, that is to say, without diplopia, without rhythmic clonicity, without lethargy, which were followed by a characteristic parkinsonian syndrome, thus indicating their epidemic encephalitic origin, since, in the absence of all diagnostic certainty we have the clinical testimony of the parkinsonism to determine a retrospective diagnosis." And later "Bringing together this case of chorea of pregnancy followed by parkinsonism and two others of which I have knowledge, which progressed in the same manner toward tremor and hypertonicity, and joining the findings of Carnal and of Harvey with the anatomicopathologic observations reported one cannot but differentiate between chorea of pregnancy and Sydenham's chorea, and connect the former, thanks to the bond of the pathognomonic parkinsonism, to epidemic encephalitis."

From the radically divergent views quoted it will be seen, as has been previously stated, that there are two main schools of thought, one regarding chorea gravidarum as merely Sydenham's chorea occurring during pregnancy, or, more rarely, vice versa, and the other regarding it as an entirely different pathologic entity, merely choreiform in type, either directly dependent on pregnancy for its causation or else a purely accidental complication of it. Our present study has caused us to align ourselves definitely with the former school and to advance the opinion that there is not one scintilla of clinical or pathologic evidence to justify any conclusion with respect to the essential nature of chorea in pregnancy except that it is Sydenham's chorea modified slightly by the associated pregnancy. Additional evidence of the indirect nature of the association is furnished by the occurrence of chorea in the puerperal period. Buist collected about 20 such cases which, however, have not been included in this series. In 3 cases in table 1 there was prompt recovery from the chorea following delivery, but a relapse occurred in a few weeks and continued for some time. It is, of course, realized that much remains unknown concerning the true nature of the ordinary adolescent type of chorea, but it is at least a well recognized clinical entity. We believe that chorea gravidarum is the same disease entity and will give our reasons for this opinion as we present the analyses of the data of our collected cases. If this be accepted as true, it follows that the term chorea gravidarum, while it has the sanction of long accepted usage is in reality a misnomer only to be justified by sanctioning such additional terms as pneumonia, typhoid and influenza gravidarum.

FREQUENCY

Chorea is one of the rarest complications of pregnancy. Our search of the literature with all the facilities of the Surgeon General's Library at our disposal has resulted in a bibliography of about 330 references

which, while it does not contain all on the subject, contains the great majority, all of any material importance and all those presenting case reports. In the effort to establish data for an estimation of its frequency in the United States, a questionnaire was sent to 530 members of obstetrical societies throughout the country. Of 170 obstetricians making returns, 53 reported that they had seen chorea gravidarum, and 117 that they had not. Of the 53 reporting cases, 14 reports were too indefinite to be used for purposes of tabulation, the remaining 39 correspondents reported a total of 104 choreic pregnancies in 85 patients. In table 2 there have been assembled all the data found in the literature or from the questionnaire bearing on the question of the frequency of occurrence of this complication in hospital or private obstetrical practice. The result is a total of 119 cases of chorea gravidarum in 270,825 pregnancies, an incidence of 1 choreic pregnancy in 2,275. In 263,625 hospital cases, there were 117 choreic pregnancies, an incidence of 1 in 2,252, as against 2 cases in 7,200 obstetrical patients seen in private practice, an incidence of 1 to 3,600.

These figures have to do with the frequency with which pregnancy is complicated by chorea. For information on the reverse of this question, namely, what proportion of cases of chorea is complicated by pregnancy, we have the data given by the "Reports of the Collective Investigation Committee of the British Medical Association" (Mackenzie), which give 9 cases of chorea gravidarum in 439 cases of chorea reported, or 1.5 per cent.

The question of the relative frequency with respect to geographical distribution is of interest and, it is believed, of importance in connection with the etiology. The reports from 13 hospitals in the United States, representing Boston, New York, Newark, N. J., Philadelphia, Baltimore, Washington, D. C., Fort Wayne, Ind., St. Louis and San Francisco, give 33 cases in 115,554 obstetrical admissions, a proportion of 1 in 3,501. Scott, from the Toronto General Hospital, reported 15 cases in approximately 2,200 admissions, an incidence of 1 in 146. In Europe, the combined reports from the Dublin Rotunda, the Frauenklinik in Leipzig and the Baudelocque Clinic in Paris give 67 cases in 105,871 admissions, an incidence of 1 in 1,580. Meyer, from the Woman's Hospital, Melbourne, Australia, reported 2 cases in 40,000 deliveries, an incidence of 1 in 20,000. A comparison of the statistics for Europe and the United States in approximately an equal number of cases shows an incidence of 1 in 1,580 for the former as against 1 in 3,501 for the latter, a relative proportion of 2.2 to 1. As throwing additional light on the frequency in Europe, it may be pointed out that the Dublin Rotunda (Sheil) is reported to have had no case in 20,000 deliveries and the Glasgow Maternity Hospital (Black) only 2 cases in a period of twenty-two years. Wall and Andrews reported 68 cases seen at the

TABLE 2—*Statistics on the Frequency of Chorea Gravidarum in a Series of Obstetrical Cases from Hospital and Private Practice*

Hospital Cases				Total Number Cases	Cases of Chorea Gravidarum	Propor- tion
Reporter*	City	Institution	Comment			
United States						
Newell	Boston	Lying In	Prior to 1901	11,000	13	1 in 846
Newell*	Boston	Lying In	Since establish- ment of clinical index	12,559	2	1 in 6,279
Phancuf*	Boston	Garney	In period of eight years		0	
Ward*	New York	Woman's		7,494	1	1 in 7,494
Williams*	Philadelphia	Maternity		1,196	0	
Tallant*	Philadelphia	Woman's Medical College	Number of cases approximate	10,000	0	
Muller*	Philadelphia	Germantown	Number of cases approximate	3,000	1	1 in 3,000
Boyd*	Philadelphia	Medico Surgical		3,600	0	
Ill*	Newark, N J	St Barnabas	Average of 300 deliveries a year		0	
Williams*	Baltimore	Johns Hopkins		16,570	11	1 in 1,506
Willson*	Washington, D C	Columbia	Number of cases approximate	30,000	2	1 in 15,000
Porter*	Fort Wayne, Ind	St Joseph's		2,975	0	
Spalding*	San Francisco	Stanford Univ		5,160	1	1 in 5,160
Berg	St Louis	City Hospital	Number of cases approximate	12,000	2	1 in 6,000
Total for United States				115,554	33	1 in 3,501
Canada						
Scott*	Toronto	Toronto General	Number of cases approximate	2,200	15	1 in 146
Europe						
Sheil	Dublin	Rotunda		20,000	0	
Gentin	Paris	Baudeloeque Clinic	1889 to 1899	15,638	15	1 in 1,042
Allard	Paris	Baudeloeque Clinic	1899 to 1919	35,882	33	1 in 1,010
Meumann	Leipzig	Frauenklinik	1886 to 1911	31,351	14	1 in 2,200
Total for Europe				105,871	67	1 in 1,580
Australia						
Meyer	Melbourne	Woman's		40,000	2	1 in 20,000
Total for hospital cases				263,625	117	1 in 2,252
Private Practice						
United States						
Mitchel*	Cincinnati			1,000	0	
Porter*	Fort Wayne, Ind		Several thou- sand cases		0	
Meyer*	Philadelphia		Number of cases approximate	2,000	0	
Kandels*	Philadelphia		Number of cases approximate	3,000	0	
Total for United States				6,000	0	
Canada						
Scott*	Toronto		Number of cases approximate	1,200	2	1 in 600
Total for private practice				7,200	2	1 in 3,600
Total for hospital cases				263,625	117	1 in 2,252
Grand total				270,825	119	1 in 2,275

* The series marked with an asterisk are from the questionnaire

London Hospital between 1882 and 1912, Shaw, 32 cases at St Mary's Hospital, Manchester, French and Hicks, the cases of 29 patients treated at Guy's Hospital, London, prior to 1906, and Cioft, 12 cases in the Women's and Children's Hospital, Leeds, "in the last few years," from the context apparently a period of six years prior to 1910. These reports from Great Britain, France and Germany are in sharp contrast to the situation in southern Europe, several Italian authors, impressed with the amount of attention given the subject in the English, German and French literature, commented on the great rarity of such cases in Italy. Only 1 case is reported for Spain, but Jakoby reported 4 cases observed in Palestine. The significance of this geographical distribution will be commented on later in connection with the association of the disease with rheumatism.

It is thoroughly realized that these statistics are of value only in a general way. There can be no question that in the United States the condition is seen much less frequently in private practice than once in 3,600 pregnancies, how much less it is impossible to say. The indicated incidence of 1 in 3,501 in hospital practice in the United States also undoubtedly gives an exaggerated idea of its frequency, as is evidenced by the previously stated fact that of 170 American obstetricians, 117 reported never having seen a case. In Great Britain the amount of literature on the subject, the number of cases reported and the statistics that have been given for several hospitals clearly indicate a greater frequency there than in this country. The most definite and reliable statistics in the literature are those from the Baudelocque Clinic, in Paris, showing 53 cases in 54,520 obstetrical admissions between 1889 and 1919, a rate of approximately 1 in a little over 1,000. Therefore, this proportion would seem to be definitely established as the frequency for this clinic, although Allard stated that these figures give an exaggerated idea of the frequency in Paris as a whole, since, as he said, "maternities are the refuge of pathological cases." The statistics of Meumann from the Frauenklinik in Leipzig, 14 cases in 31,351 admissions, or 1 in 2,200, show a frequency of somewhat less than one-half that of Paris. The statistics of Scott from the Toronto General Hospital, 15 cases in approximately 2,200 obstetrical admissions, or 1 case in 146, are so out of proportion to all other reports that we are at a complete loss to explain them.

ETIOLOGY

Age—The age of the patient was definitely stated in 666 cases, the resulting average age being 22.4 years. In chart 1, the age distribution by years is graphically represented in percentages of the total number of cases, and for comparison the same is done for 2,000 white women

delivered at Columbia Hospital for Women, Washington, D C In chart 2, the same comparison is presented in percentages between the age distribution by hemidecades of 670 choreic cases and the 2,000 cases mentioned It will be observed that the curve of the choreic cases shows

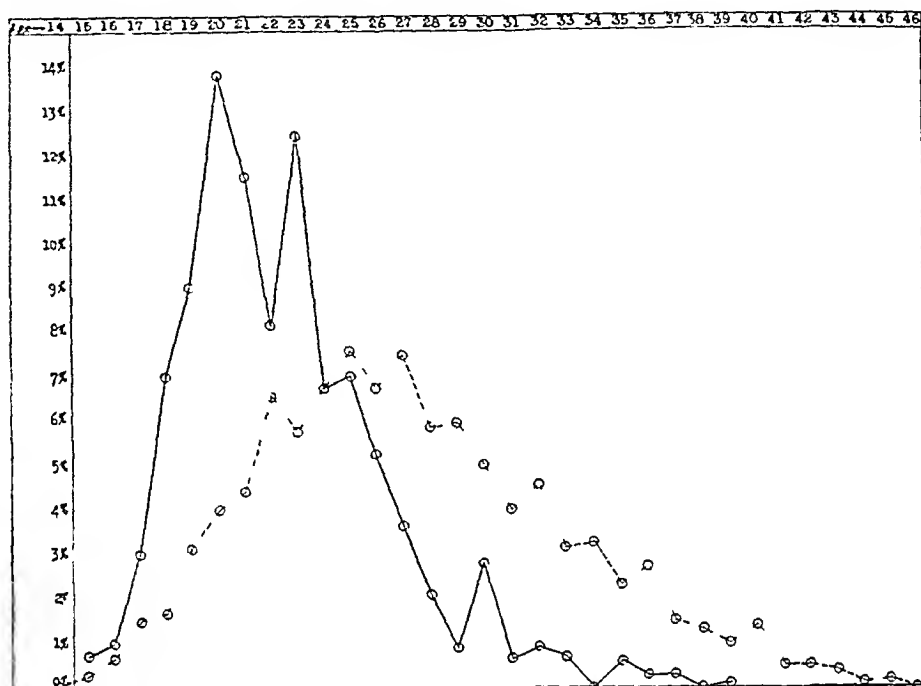


Chart 1—Comparative age distribution, by years, in percentages of the total number of cases, between 666 collected choreic and 2,000 nonchoreic pregnancies in white women from Columbia Hospital, Washington, D C The solid line indicates choreic cases, the dotted line, nonchoreic cases

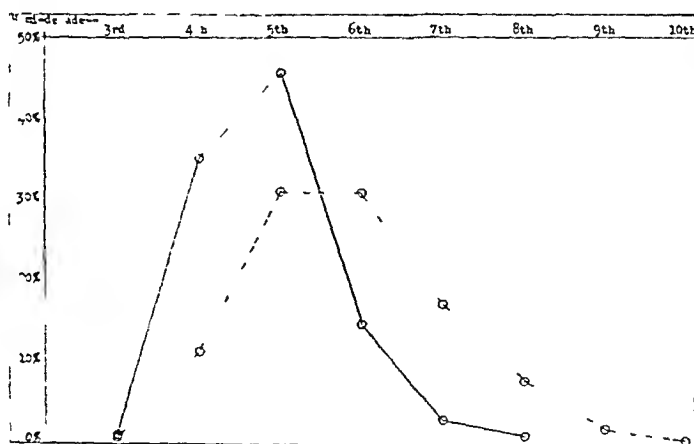


Chart 2—Comparative age distribution, by hemidecades, in percentages of the total number of cases, between 670 collected choreic and 2,000 nonchoreic pregnancies in white women from Columbia Hospital, Washington, D C The solid line indicates choreic cases, the dotted line, nonchoreic cases

a much larger percentage distributed in the early twenties than does the curve of the control series. The former reaches its peak at the twentieth year, the latter not until the twenty-fifth, while the decline from the peak is much more precipitate in the former than in the latter. In chart 2 it will be observed that the choreic cases exceed the controls in the third, fourth and fifth hemidecades by 0.3, 24 and 14.5 per cent, respectively while in the sixth, seventh and eighth hemidecades the controls exceed the choreic cases by 17, 14 and 7 per cent. In the ninth hemidecade, 1.75 per cent of the controls was found as against none of the choreic pregnancies. A comparison by decades shows 35.9, 60.2 and 3.7 per cent of the choreic cases distributed in the second, third and fourth decades of life as against 11.4, 61.6 and 25.1 per cent of the controls. If, however, the comparison is made for the first, second and third decades of sexual maturity, the difference is found to be even more striking, as evidenced by the following figures: 74.7, 23.8 and 1.3 per cent of the choreic cases as against 34.7, 53.1 and 11.9 per cent of the controls.

TABLE 3—*Parity in Seven Hundred and Forty-Six Cases*

Number of cases	Para													Multiparae
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	
	414	171	73	38	19	8	2	2	1	1	1	1	2	13

These figures would seem to show conclusively that chorea complicating pregnancy is a disease of young women. In this respect the disease is in accord with Sydenham's chorea, which, as is well known, usually attacks children and young adolescents.

Social Status—Data on the legitimacy or illegitimacy of the pregnancy were available in 505 cases. Of these, 418 pregnancies were legitimate and 87 illegitimate, an illegitimacy rate of 17.2 per cent. The statement has been made that chorea is more frequent in illegitimate pregnancy, but, while the foregoing rate does seem high, there is obviously no way to check it against any comparable series of cases.

Parity—The data in 746 cases are available for studying the question of parity distribution. This material has been tabulated in table 3 from which the predominance of the first pregnancy may be seen at a glance. It must be borne in mind, however, as will be seen by reference to table 1, that of the total of 951 choreic pregnancies there were 253 that occurred in 99 persons. This well demonstrated tendency of the disease to attack the same patient in more than one pregnancy has seemed to indicate a further study of the material to determine the parity distribution by percentages, of the total number of patients suf-

fering from their first attack of chorea gravidarum. Data on this point were available in 509 cases and have been assembled in graphic form in chart 3, together with a similar study, for comparison, of 2,000 nonchoreic pregnancies from Columbia Hospital for Women, Washington, D C. It will be seen that in the choreic cases primiparae exceed the controls by 30.5 per cent and are decidedly exceeded by the controls in every other pregnancy.

History of Chorea Previously—It now becomes necessary to consider the question of the previous history of the patients with respect to chorea. In this connection, the cases were divided into three groups,

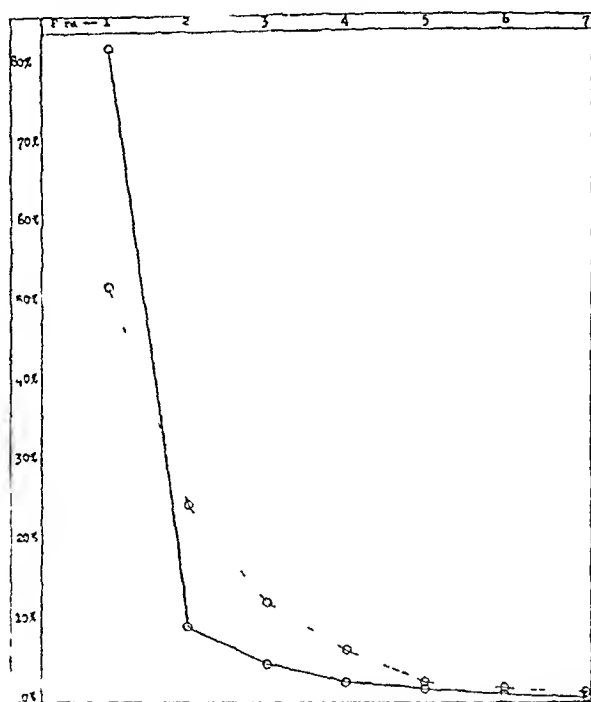


Chart 3—Comparative parity distribution in percentages of the total number of cases, between 509 first attacks of chorea gravidarum and 2,000 nonchoreic pregnancies in white women, from Columbia Hospital, Washington, D C. The solid line indicates choreic cases; the dotted line, nonchoreic cases.

namely: Those in which a previous history of chorea was definitely denied, those in which it was admitted and in which, from the context, it could be determined that this was ordinary chorea and not chorea gravidarum and, finally, those giving a history of a previous chorea which, from the context, could not be definitely so classified. The data of 474 cases were available for this study and are tabulated in table 4. From this table it will be seen that in 474 cases of chorea gravidarum there were 185 patients who definitely denied previous chorea or 39 per cent; 228 who gave a history of previous chorea

unassociated with pregnancy, or 48.1 per cent, and 61 who gave a history of previous chorea, the relation of which to pregnancy could not be determined, or 12.8 per cent. It would seem to be quite obvious that in the majority of cases in this last group the previous history of chorea referred to ordinary chorea and not to chorea gravidarum, since the occurrence of this complication in more than 1 pregnancy would almost inevitably cause comment by the reporter. On adding these two groups together, the percentage of patients giving a history of previous chorea is increased to 60.9 per cent. But even this figure does not quite give the whole picture. These figures all refer to individuals. If we examine the statistics for pregnancies, rather than individuals, and include the cases in which chorea complicated more than 1 pregnancy as separate choreic pregnancies with a history of previous chorea, we arrive at the following figures. In 628 choreic pregnancies chorea had occurred previously in 443, or 70.5 per cent, and had not

TABLE 4—*History of Four Hundred and Seventy-Four Patients Concerning Previous Choreia*

	No of Cases	Percentage
No chorea previously	185	39.0
History of previous chorea not associated with pregnancy	228	48.1
History of previous chorea, association with pregnancy not determined	61	12.8
Total	474	99.9

occurred in 185, or 29.4 per cent. These figures may be compared with those given by Allard from the Baudelocque Clinic, which showed previous attacks of chorea in 81 per cent of 53 cases.

The opposite question as to the number of women, choreic in childhood or adolescence, in whom chorea develops in a subsequent pregnancy is answered in the literature only by the author just quoted. The statistics of the Baudelocque Clinic show that in 38,382 obstetrical admissions there were 201 patients who gave a history of previous chorea, and of these, 53 had chorea gravidarum. This would indicate that approximately 25 per cent of women who have had chorea in childhood may be expected to have a recurrence during pregnancy.

It seems reasonable to believe that these facts can be explained only on the hypothesis that pregnancy causes a latent disease to become active, any other theory certainly involves overlooking the obvious. Furthermore, it has been shown that chorea occurring for the first time during pregnancy may, and often does, complicate subsequent pregnancies and may finally continue indefinitely post partum.

Association with Rheumatism.—In order to study the association of chorea gravidarum with rheumatism, the cases were divided into

four groups as follows. First, those in which a history of previous rheumatism was definitely denied; second, those in which it was definitely admitted; third, those in which the rheumatic history was dubious; and, fourth, those in which there was a double complication with chorea and rheumatism in the same pregnancy. There were 404 cases available for this study, which are tabulated in table 5. From this table it will be seen that in 35.3 per cent of 404 cases there was a history of previous rheumatism, while in 4.4 per cent of the cases the choreic pregnancy was also complicated by rheumatism. In this latter group, made up of 18 cases, the rheumatism was synchronous with the chorea in 12 cases, preceded it in 5 cases and followed it in 1 case. By placing these two groups together, we arrive at the figure of 39.7 per cent of the cases either associated with rheumatism or giving a history of it. The real figures may well be in excess of these, however, for, as pointed out by Duckworth, the milder manifestations of rheu-

TABLE 5—*Association of Chorea Gravidarum with Rheumatism in Four Hundred and Four Cases*

	No. of Cases	Percentage
History of previous rheumatism negative	237	58.6
History of previous rheumatism positive	143	35.3
History of previous rheumatism doubtful	6	1.4
Rheumatism associated with chorea in same pregnancy	18	4.4
Total	404	99.7

matism in childhood usually escape memory. Certain cases in table 1 throw an additional light on this subject. Thus there is the patient of Semple who had never had chorea but who had acute rheumatic fever a few months before her first pregnancy, in which chorea developed in the first month. The patient of Black had chorea in childhood and a first pregnancy that was normal; later she had acute rheumatic fever, and following this the second and third pregnancies were complicated by chorea. Matthews and Randle each reported the case of a patient with three normal pregnancies, then acute rheumatic fever and chorea in the fourth pregnancy. Genova reported the cases of two patients with four normal pregnancies, then rheumatic fever and chorea in the fifth pregnancy, and Villapadierna reported the case of a patient with the same sequence of events following five normal pregnancies. The patient of Hunnicut had an attack of acute articular rheumatism complicating the puerperium.

The association between rheumatism and Sydenham's chorea is too well known to require comment; the Collective Investigation Committee of the British Medical Association found a definite history of it in 26 per cent and an indefinite history in 14 per cent of their cases.

A comparison of these findings with those just given for chorea gravidarum shows that the incidence of rheumatism in the two series is practically identical. In connection with the association of the disease with rheumatism, its geographical distribution is significant. It has been shown that it is particularly prevalent in Great Britain, to a somewhat less extent in Germany and France, and that it is very rare in southern Europe. Surgeon General Cumming of the Public Health Service is my authority for the statement, significant in this connection, that of all immigrants inspected at Ellis Island, those from Great Britain and Ireland show the highest proportion of rheumatic sequelae.

History of Both Chorea and Rheumatism Previously—In 339 cases, the histories were definite regarding both chorea and rheumatism.

TABLE 6—*History of Three Hundred and Thirty-Nine Patients with Respect to Both Chorea and Rheumatism*

	No. of Cases	Percentage
Neither chorea nor rheumatism previously	115	33.9
Both chorea and rheumatism previously	101	29.7
Chorea previously without previous rheumatism	101	29.7
Rheumatism previously without previous chorea	22	6.5
Total	339	99.8

TABLE 7—*Frequency of Cardiac Disease in Three Hundred and Fifty-Eight Cases*

	No. of Cases	Percentage
Heart normal	183	51.1
Heart definitely diseased	116	32.4
Evidence of disease questionable	59	16.4
Total	358	99.9

These data are given in table 6, from which it will be seen that in over one fourth of the pregnancies there is a history of both chorea and rheumatism, and in approximately two thirds of them of one or the other or both. It should be further noted that in 24 patients giving a positive history of both diseases previously, there was also definite evidence of cardiac disease.

Evidence of Cardiac Disease—On this point the available material is made up of 358 pregnancies that have been classified into three groups, namely: Those in which the heart was definitely stated to be normal, those in which there was either definite pathologic evidence of heart disease or a sufficiently detailed clinical report to justify the assumption that disease was present and those in which the clinical evidence presented tended to indicate disease, but was deemed insufficient to make a positive diagnosis. These data are given in table 7.

It will be seen from these figures that heart disease was definitely noted in approximately one third of the cases or, if we include the group of cases with indefinite evidence of disease, more or less definitely in approximately one-half. These findings coincide closely with those for ordinary adolescent chorea reported by Strong, according to whom, in a series of 2359 cases reported by 9 authors, there was evidence of organic cardiac disease in 953, or 40.3 per cent. Thus we have demonstrated again a striking similarity between these two types of chorea.

Emotional Disturbance Before the Attack—In the ordinary chorea of childhood, fright, overstudy, etc., have often been accepted as the immediate predisposing cause of an attack. In 68 cases of chorea gravidarum in this series some form of emotional disturbance, fright, anger, worry, etc., was stated to have preceded the outbreak.

Rarity in the Negro—Sydenham's chorea is excessively rare in the Negro race, and no case of chorea gravidarum in a Negress is reported in the literature. Too late for incorporation in our statistics, however, a patient with a mild but quite typical case has been admitted to the Georgetown University Hospital.

PATHOLOGY

The data available for study of the pathology are found in the more or less complete reports of 67 autopsies found in the literature from 1824 to 1930, inclusive. As might be expected, much of this material is of little value from the point of view of the modern histopathology of the nervous system, but even the older records contribute some information of value. Interest naturally centers in the heart and central nervous system, but the pathology in other organs must be briefly considered first.

The liver is stated to have been normal in 5 instances, and was the site of parenchymatous degeneration in 3 cases, cloudy swelling twice, congestion once and several small areas of necrosis once. The spleen is reported normal in 5 instances, and was the site of softening once, hyperplasia twice, marked swelling once, passive congestion once, infarcts once and embolism twice. The kidneys are reported normal in 4 cases and were the site of congestion 5 times, parenchymatous nephritis 4 times, bacterial infarcts once, cloudy swelling twice, fatty degeneration once, embolism 3 times and pyelitis once. The lungs were reported normal 4 times, and the site of congestion 4 times, edema twice, bacterial infarcts once, bronchopneumonia twice, pneumonia and pleurisy once and subpleural hemorrhages once. The uterus and adnexa gave evidence of puerperal infection in 5 instances. Fragmentary as this evidence is it would seem to point toward an underlying pathology of an infectious nature.

The most striking finding in the autopsy material was the great frequency of cardiac disease. The condition of the heart was mentioned in 46 cases, in 40 of which it was diseased and in only 6 apparently normal, an incidence of cardiac pathology of 86.9 per cent. The most frequent finding was acute, recent endocarditis, often described as ulcerative or vegetative, the mitral valve being the favorite site. Less frequently the disease was described as chronic, or thickening or distortion of the valve flaps was the only pathology present. Myocarditis was present in several instances, but except for ecchymoses beneath it, the pericardium does not seem to have been involved.

In the central nervous system the most frequently mentioned macroscopic finding is congestion of the brain and meninges. This was almost universally noted. Edema was mentioned twice, scattered petechial hemorrhages twice, increased cerebrospinal fluid 3 times, pachymeningitis twice, hemorrhage in 1 case, purulent leptomeningitis once, embolism of the left middle cerebral artery in 2 cases, in 1 of which the embolus lodged beyond the anterior choroid branch and was of the same material as the vegetation on the mitral valve, and there was also an extensive hemorrhage resulting from a rupture of one of the smaller branches of the middle cerebral artery supplying the corpus striatum, thrombosis of several cerebral sinuses once, and in 5 cases the brain was reported as normal. In 10 examinations of the spinal cord, it was reported to be normal 4 times, congestion was noted in the other cases, with an acute inflammation of the meninges once and softening of the cord structure in 4 instances.

The number of studies of the histopathology of the brain are as yet entirely too few to permit any final deductions as to the exact nature of the pathologic changes. They may be summarized as follows:

Elischer (1874), in a patient dying four days post partum, found degeneration in the central ganglions, insula and claustrum, secondary extravasations in the neuroglia with small emboli, congestion of the spinal meninges, and changes in the nerve cells in the cord.

Guinon (1886) reported the brain normal microscopically.

Turner (1892) presented colored plates showing 2 pyramidal cells from the deeper cortical layers of the Rolandic area which were swollen and deformed, with granular cytoplasm, deformed and abnormally stained nuclei, and, in a single instance, loss of the cell outline.

Pelnař (1904), in the case of a woman who died with high fever and fulminating sore throat, found marked congestion of the brain with small hemorrhages, but no evidence of encephalitis. "Chorea bodies" were present, but were considered to be artefacts.

Poynton and Holmes (1906), in a case reported by French and Ricks, found recent thrombi in many vessels around some of which the brain tissue was slightly necrosed and infiltrated with serum. There was some small round cell infiltration into the vessel walls and perivascular lymph spaces. Marked degenerative lesions were noted in the nerve cells. "Micrococci, generally lying as diplococci

were found after careful searching in the pia mater of the fore brain and in the walls of the cerebral vessels"

De Crespigny (1913), in the case reported by Wilson, found numerous scattered capillary hemorrhages from the vessels of the leptomeninges and throughout the substance of the cerebrum. There was intense congestion of the capillaries. The brain was not sufficiently well fixed to enable changes in the nerve cells to be described, if such were present.

Schuster (1920), in a case in which *Staphylococcus aureus* had been cultured from the blood, found thrombosis associated with hemorrhage in the third frontal and ascending frontal convolutions of the right parietal lobe. The condition of the nuclei of the base was not mentioned. There was also hyperplasia of the neuroglia of the cerebral cortex.

Marie, Boutier and Tretiakoff (1923) presented one of the most complete and extensive histopathologic studies in the literature. They said "The histologic examination of the nervous centers discloses the existence of two parallel pathologic processes, an exudative meningitis, accompanied by an abundant hemorrhagic exudate in the adventitial coats of the vessels of the base of the brain, and numerous small toxic-infectious nodules disseminated in the cerebral mass." The meningeal exudate contained much fibrin, and the red cells greatly predominated over the leukocytes. The endothelial cells of the vessel walls were irritated and proliferated, but the walls were intact. In the cerebral cortex numerous toxic-infectious nodules of the size of a pinhead were found, made up of proliferated neuroglia cells surrounding one or two capillaries, some containing granules of myelin. At the site of the nodules the nerve cells are distinctly altered and some axis cylinder processes are altered and capped by terminal enlargements, and the adjacent tissues are edematous. "To summarize, there are small nodular lesions, destructive (or degenerative), where the phenomena of reaction are reduced to edema and a proliferation of neuroglia cells, the influence of leukocytes is entirely absent." In the centrum ovale and the corpus optostriatum, the same two pathologic processes were noted. "The sub-optic region, the cerebral peduncles, the medulla and the cerebellum seemed to be spared by the morbid process."

Creutzfeldt (1924) found intense congestion of the meninges with several military hemorrhages. In the brain, particularly in the corpus striatum and especially its anterior and subependymal portion, the tuber cinereum, the cerebellum, the medulla and the internal capsule, there were noted, disposed in islets, perivascular infiltrations of two varieties, inflammatory and degenerative, with the degenerative lesions predominating. In the white matter there were also encountered some foci of cellular necrosis and other foci characterized by a disappearance of myelin and the presence of granular bodies and, sometimes, of perivascular infiltrations, surrounded by areas of hypertrophy and hyperplasia in the neuroglia. The maximum of these lesions was found in the corpus striatum, and especially in the putamen, involving the small cells. In the body of Luys many cells had disappeared, in the nuclei of the tuber and the dentate nucleus, the lesions were less numerous.

Urechia and Elekcs (1925) found "Congestion of the meninges and brain with many foci of embolic necrosis and pericapillary hemorrhage in the caudate nucleus. In many places the vessels are filled with micrococci. Most of the lesions are found in the corpus striatum and particularly in the caudate nucleus. After this and in a decreasing order. Olivary nucleus, body of Luys, and bulbar olive. In the other nuclei the lesions are slight."

These last authors quoted A. Jacob (1923), the reference for whose article could not be found as noting "emboli with resulting necroses, in the brain

involving particularly the putamen and the caudate nucleus" Coexistent with the necrosis, he noted in these areas a hypertrophy with proliferation of the neuroglia

Von Lehoczkv-Semmelweis (1926) reported the observations of a microscopic study of a brain made in the Neuro-Histological Institute of Professor Shaffer These were "marked perivascular infiltration of the corpus striatum, the thalamus and the substantia nigra The cellular elements of the infiltrate were chiefly lymphocytes, although there were also plasma cells and, in the substantia nigra, there were macrophages filled with brown pigment A more important finding was a marked dissolution of the nerve cells in the putamen and in the globus pallidus The process was more marked in the latter With this condition in the putamen and in the pallidus there was a very pronounced proliferation of the glia which in part was localized and in part diffused These partly degenerative and partly inflammatory changes can very well be rationalized with the disease process since, in the case of chorea, alterations of individual parts of the extrapyramidal systems are commonly observed In this case the disease began during pregnancy with fever and complaint of polyarthritis All these factors, together with the anatomic observations, support the conception that we are not here dealing with an intoxication of pregnancy, but with an infection similar to chorea in which the lesions responsible were so severe that the artificial termination of the pregnancy did not save the life of the patient"

Winkelman (1926) described the histopathology of the brain as follows "The meninges show a relatively marked connective tissue proliferation and a slight lymphocytic infiltration which is to some extent perivascular The structure of the cortex is everywhere disturbed Here and there one finds certain blood vessels with a very slight perivascular infiltration of lymphocytes The ganglion cells show mostly a moderate chromatolysis and edema The glia cells appear to be only slightly increased in number Preparations stained with scarlet red show only a slight content of lipoid in the ganglion cells and the walls of the blood vessels With the low power one can see alterations in the smaller vessels and in the Nissl granules With higher magnifications one can tell that these appearances are due not only to perivascular infiltration, but also to proliferation of the elements of the vessel wall The endothelial cells and the adventitia cells are swollen and proliferated, resulting in a narrowing of the lumen This narrowing is so marked that in many vessels the lumen is obliterated The endothelial cells of the smallest capillaries are very much swollen It can be recognized that these changes are most marked in the corpus striatum, although they are frequently noted in the cortex The striatum appears to be unmistakably the chief site of the changes Its normal structure has become altered To be sure, the large ganglion cells have not diminished and are nearly normal Many of them are surrounded by 'Trabantzellen, which, however, is a normal finding Others may be found with swollen, washed out protoplasm, but with no nuclear changes On the contrary, the smaller ganglion cells show marked alteration They are diminished in number, many are swollen with indistinct outlines, and in many the nuclei have quite disappeared Others stain deeply and homogeneously Small groups of glia cells can be seen where previously ganglion cells were to be found In other respects there is not much to add to the foregoing description The glia has markedly proliferated, which is especially to be observed in Cajal preparations As in the cortex, the small blood vessels are easily observed on account of their thickened walls Here and there one sees a slight perivascular infiltration of lymphocytes Marked infiltration about the blood vessels is rare

"The caudate nucleus shows more changes than the putamen The glia is even more markedly proliferated, and under the ependyma of the ventricle one finds a

stretch of glia where the ganglion cells are much diminished and altered. Here and there blood vessels are visible the lymph spaces of which are enlarged by edema and filled with transudate.

'In the globus pallidus severe parenchymatous changes are missing, and in the blood vessels one sees the same changes as in the rest of the central nervous system. There are no precipitates or calcium-like material.

'Fat stains show nothing unusual either in the corpus striatum or in the globus pallidus. The iron content is apparently normal.

"The cells of the thalamus show acute changes in the Nissl granules. There is possibly some increase in the glia. Around the third ventricle one finds small fresh hemorrhages, especially around the blood vessels. The walls of the blood vessels have here the same changes as those described. In the subthalamie region there are the same changes as in the thalamus with possibly more pronounced perivascular infiltration and more frequent hemorrhage. Around many blood vessels one sees many 'Gitterzellen' with green pigment. The substantia nigra was not to be found. The choroid plexus was normal. The pons, medulla and cerebellum showed thickening of the blood vessels and at times perivascular infiltration, apart from these they were normal. The cells of the dentate nucleus and the olive were normal. Nowhere in the central nervous system is there evidence of embolism or thrombosis."

From these histopathologic observations, the microscopic changes in the brain and meninges may be briefly summarized as follows. There is an intense congestion, not infrequently associated with petechial hemorrhage and some thrombosis. The perivascular reaction is predominately degenerative rather than inflammatory, and leukocytic infiltration is slight or entirely lacking. The neuroglia is hyperplastic, and necrobiotic changes are present in both the nerve cells and their processes. These changes reach their quantitative and qualitative maximum in the corpus striatum, especially the caudate nucleus, they are also present to a less degree in the cerebral cortex and the other nuclei of the base.

From the foregoing descriptions of the histopathology of the brain it will be seen that knowledge of this subject for chorea gravidarum is in the same state of uncertainty that obtains for Sydenham's chorea in adolescents. Marie, Boutier and Trétiakoff felt justified, on the histopathologic picture present, in differentiating their case from ordinary chorea on the one hand and epidemic encephalitis on the other. Urechia and Elekes, on quite similar findings, thought that their case lent support to those who held the two types of chorea to be identical, and they quoted Lewy as holding this view after studying the pathology of each. Sicard, as has been seen, expressed the belief that the pathologic evidence, supported by the occurrence of a parkinsonian syndrome following three cases, is sufficient to place chorea gravidarum as a manifestation of epidemic encephalitis, mainly, apparently, because he had never seen parkinsonism follow the chorea of childhood. In the one point in the cerebral pathology on which there seems to be

general agreement for both types of chorea, namely, the predilection of the lesions for the corpus striatum, the two diseases correspond exactly

The evidence furnished by the general pathology certainly points most definitely toward an infectious origin of the condition, which, again, is in agreement with the consensus regarding Sydenham's chorea. This view of the matter is further supported by the findings with respect to the heart. An incidence of cardiac pathology, mostly acute endocarditis, of 86.9 per cent in forty-six hearts examined, certainly speaks for an infectious origin of the disease, accentuates its relation to rheumatism and, taken alone, would seem to justify the conclusion that the condition has no relation to epidemic encephalitis. It will also be observed that the pathologic evidence lends no support to the opinion that the toxemia of pregnancy stands in any etiologic relationship to chorea gravidarum.

(To be Concluded)

RED CELL REGENERATION DURING THE MENSTRUAL CYCLE^{*}

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AND

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NEW YORK

In the human female the process of menstruation is accompanied by a train of phenomena of which the uterine changes are only a part. Thus pain and nervous and congestive reactions may at times become very pronounced. These various activities of the organism usually increase in intensity a few days before the menstrual flow begins to diminish again toward the close of the period. A second lesser maximum may occur a few days after the flow has ceased. Naturally much attention has been centered on the changes in the peripheral blood and blood-forming organs during menstruation but the reports have been somewhat confusing. The quantity of blood lost during a normal period is also a subject of considerable discussion. Kelly¹ stated that the amount is from 60 to 240 cc, Crossen² gave it as from 150 to 300 cc and Howell,³ from 100 to 200 cc while Hoppe Seyler⁴ was convinced that the quantity is greatly overestimated and rarely exceeds 37 cc. He arrived at this conclusion by soaking in water all the napkins used during a single period and determining the amount of hemoglobin in the solution.

The erythrocyte changes during the menstrual cycle have been studied by Detre,⁵ who found an increase during the premenstrual stage reaching the highest values just before the beginning of menstruation.

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1 Kelly, H A Gynecology, New York, D Appleton & Company, 1928, p 118

2 Crossen, H S Diseases of Women, St Louis, C V Mosby Company, 1930, p 829

3 Howell, W H A Text Book of Physiology, Philadelphia, W B Saunders Company, 1927, p 1004

4 Hoppe Seyler Ueber den Blutverlust bei der Menstruation, Ztschr f physiol Chem 42 545, 1904

5 Detre L Ztschr f d ges exper Med 59 240 1928

This is followed by a gradual decrease, and the lowest values are reached in the postmenstrual period. According to Polzl,⁶ there is an increase in the number of red blood cells, sometimes of from 1,000,000 to 1,500,000. This decreases with the onset of the flow. Reinert,⁷ Hayem⁷ and Reinl⁷ agreed with these findings, as did Blumenthal⁸ and Kurtschenkoff⁷. It is the opinion of Holler, Melicher and Reiter⁹ that there is a hyperfunction of the bone marrow in the premenstrual phase, and that the increase in erythrocytes is an expression of this hyperfunction. Their method for determining the bone marrow function was not mentioned in the paper. Since no references to histologic studies or reticulocyte counts are made in their report, their conclusions are not determinative. These authors also found similar changes in the hemoglobin, but not as definitely as changes in the red cells. The changes in the hemoglobin seemed to follow the variations in the red blood cells. Further support of this view is voiced by Piney,¹⁰ who stated that there seems to be no doubt that a reduction in the number of erythrocytes occurs at the time of menstruation, and this may be quite considerable in degree. Furthermore, he said that the diminution in the number of the red blood cells is definitely greater than could be explained by the menstrual loss of blood. He was not so certain that a rise in the number of red cells occurs before menstruation. In contrast, Merletti¹¹ found a decrease in the premenstrual erythrocyte values, and Gumprich and Davidovitsch¹² described variations in the red blood count during menstruation which were not definite.

For the present experiment, six relatively normal young women were chosen, on whom blood counts (hemoglobin and red blood cells) were done twice a week for a period of three months. The percentage of reticulocytes was also determined each time, since it is now well known that the number of reticulocytes in the peripheral blood is a reliable index of bone marrow activity. It was planned to observe the changes in the hemoglobin, red blood cells and reticulocytes over a longer time than in any of the previous reports and thus obtain a better idea of the erythrocyte changes in the blood and bone marrow coincident with the various phases of the menstrual cycle.

6 Polzl. *Wien klin Wchnschr* **7** 238, 1910

7 Quoted by Gumprich, G. *Einfluss der Menstruation auf das Blutbild bei gesunden Individuen, Beitr z Geburtsh u Gynak* **19** 435, 1913-1914

8 Blumenthal. *Beitr z Geburtsh u Gynak* **61** 614, 1908

9 Holler, G., Melicher, H., and Reiter, N. *Ztschr f klin Med* **100** 564, 1924

10 Piney, A. *Recent Advances in Hæmatology*, Philadelphia, P. Blakiston's Son & Company, 1927, p 180

11 Merletti. *Beitr z Geburtsh u Gynak* **19** 459, 1914

12 Gumprich (footnote 7)

TECHNIC

All hemoglobin determinations were made with one Sahli instrument, after standardization against the Van Slyke oxygen-combining method. Red counts were done with two standardized pipets. Separate drops from the two pipets were counted for each determination, and the results were accepted only if the counts checked within 200,000 red cells. These two counts were then averaged, and the result was taken for the final reading, thus reducing the error to about 2 per cent. Reticulocytes were counted on cover slip preparations vitally stained with brilliant cresyl blue and counterstained with Wright's stain. For each reticulocyte count, at least 10,000 red cells were examined, after the suggestion of Krumbhaar¹³. This was done by estimating the average number of red blood cells in a field and then counting by fields until the desired number had been reached. The percentage of reticulocytes was then calculated. The foregoing method gives more uniform results than the usual count of 1,000 red cells.

RESULTS

The experimental data are given in the table

Results of Experiments

Case 1				Case 2			
Date	Hemo globin, per Cent	Red Blood Cells, Millions	Reticulo cytes, per Cent	Date	Hemo globin, per Cent	Red Blood Cells, Millions	Reticulo cytes, per Cent
1/20	75	4.2	0.3	1/20	82	3.8	0.1
1/23	80	4.2	0.1	1/23	81	4.9	0.3
1/27	71	3.8	0.2	1/27	87	4.6	0.4
1/30	74	3.9	0.3	1/30	82	4.0	0.2
2/ 3	73	3.9	0.3	2/ 3	85	4.0	0.2
2/ 6	78	3.9	0.1	2/ 6	84	4.4	0.2
2/10	84	4.0	0.1	2/10	85	4.4	0.12
2/13	77	4.1	0.2	2/13	87	4.7	0.26
2/17	71	4.3	0.2	2/17	88	4.3	0.52
2/20	79	3.7	0.08	2/20	84	4.4	0.21
2/25	75	4.3	0.16	2/25	93	4.3	0.22
2/27	80	4.9	0.11	2/27	92	4.9	0.31
3/ 3	84	4.0	0.12	3/ 3	90	4.7	0.28
3/ 6	84	4.2	0.09	3/ 6	93	4.8	0.29
3/10	93	4.6	0.08	3/10	89	4.3	0.4
3/11	76	4.2	0.1	3/13	89	4.7	0.13
3/17	80	4.1	0.07	3/17	85	4.1	0.53
3/21	81	4.3	0.09	3/21	85	4.2	0.26
3/25	83	4.1	0.12	3/25	92	4.7	0.3
3/27	80	4.0	0.16	3/27	85	4.1	0.27
3/31	82	4.3	0.11	3/31	91	4.4	0.15
4/ 3	86	4.5	0.04	4/ 3	80	4.4	0.35
4/ 7	85	4.3	0.03	4/ 7	81	4.5	0.17
4/10	79	4.2	0.09	4/10	95	4.2	0.14
4/14	85	4.4	0.04	4/14	88	4.3	0.3
4/17	85	4.0	0.08	4/17	90	4.7	0.4
4/21	84	4.1	0.16	4/21	85	4.2	0.1
4/24	85	4.9	0.21	4/24	84	4.3	0.25
							Menstrual period 1/17 1/21
			Menstrual period 2/11 2/16				
							Menstrual period 3/6 3/10
			Menstrual period 3/10 3/15				
							Menstrual period 4/2 4/7
			Menstrual period 4/14 4/19				

Date	Hemo globin, per Cent	Red Blood Cells, Millions	Reticulo cytes, per Cent		Date	Hemo globin, per Cent	Red Blood Cells, Millions	Reticulo cytes, per Cent	
<i>Case 3</i>					<i>Case 4</i>				
1/20	90	5.2	0.2		1/20	78	4.7	0.1	Menstrual
1/23	90	4.7	0.3		1/23	80	4.9	0.2	period 1/20 1/25
1/27	93	4.2	0.4		1/27	77	4.3	0.1	
1/30	90	4.9	0.3		1/30	78	4.6	0.2	
2/ 3	95	5.0	0.2		2/ 3	83	5.4	0.3	
2/ 6	86	5.2	0.4		2/ 6	80	4.7	0.1	
2/10	88	5.0	0.3	Menstrual	2/10	90	5.1	0.08	
2/13	90	5.1	0.2	period 2/10 2/13	2/13	83	4.8	0.11	Menstrual
2/17	100	5.0	0.23		2/17	90	4.7	0.19	period 2/13 2/18
2/20	100	5.2	0.20		2/20	92	4.7	0.13	
2/25	92	5.6	0.04		2/25	92	5.3	0.11	
2/27	90	5.5	0.26		2/27	90	4.9	0.09	
3/ 3	90	5.1	0.21		3/ 3	96	4.8	0.20	
3/ 6	93	5.0	0.20		3/ 6	88	5.1	0.08	
3/10	98	5.5	0.21	Menstrual	3/10	91	5.0	0.06	Menstrual
3/13	106	5.5	0.17	period 3/10 3/13	3/13	86	4.8	0.06	period 3/12 3/17
3/17	97	5.2	0.21		3/17	90	4.8	0.18	
3/21	100	5.4	0.13		3/21	87	4.6	0.12	
3/25	92	5.2	0.17		3/25	94	4.8	0.22	
3/27	98	5.0	0.15		3/27	90	4.5	0.06	
3/31	93	5.1	0.2		3/31	92	5.1	0.13	
4/ 3	94	5.0	0.36		4/ 3	87	4.8	0.22	
4/ 7	93	5.1	0.10	Menstrual	4/ 7	83	4.8	0.10	Menstrual
4/10	90	5.4	0.24	period 4/7 4/10	4/10	94	5.5	0.09	period 4/8 4/14
4/14	90	4.9	0.14		4/14	90	4.9	0.11	
4/17	102	5.5	0.12		4/17	90	4.5	0.39	
4/21	99	5.2	0.16		4/21	87	4.7	0.11	
4/24	99	5.3	0.19		4/24	92	5.0	0.18	
<i>Case 5</i>					<i>Case 6</i>				
1/20	85	4.5	0.2		1/20	89	4.4	0.1	
1/23	84	4.9	0.1		1/23	89	5.0	0.09	
1/27	87	5.0	0.4		1/27	75	4.3	0.10	
1/30	90	5.4	0.2		1/30	82	4.8	0.20	
2/ 3	90	5.2	0.1		2/ 3	82	4.7	0.1	
2/ 6	89	5.0	0.3		2/ 6	82	4.2	0.2	
2/10	87	5.0	0.13		2/10	85	4.4	0.18	
2/13	82	5.0	0.25		2/13	91	4.7	0.08	
2/17	94	4.8	0.03		2/17	86	4.8	0.07	Menstrual
2/20	96	5.0	0.24		2/20	91	4.7	0.02	period 2/19 2/23
2/25	93	5.1	0.07		2/25	83	4.3	0.03	
2/27	95	4.8	0.28		2/27	85	5.1	0.09	
3/ 3	91	5.4	0.4	Menstrual	3/ 3	80	4.3	0.2	
3/ 6	93	5.0	0.14	period 3/1 3/6	3/ 6	89	4.2	0.08	
3/10	100	5.0	0.25		3/10	89	4.8	0.09	
3/13	101	5.4	0.21		3/13	76	4.5	0.09	Menstrual
3/17	92	5.5	0.25		3/17	91	4.6	0.06	period 3/13 3/17
3/21	95	5.5	0.24		3/21	80	4.5	0.12	
3/25	98	5.1	0.26		3/25	84	4.6	0.12	
3/27	90	5.1	0.34		3/27	84	4.8	0.12	
3/31	90	5.1	0.52		3/31	85	4.7	0.08	
4/ 3	88	5.6	0.26	Menstrual	4/ 3	90	4.6	0.13	
4/ 7	87	4.8	0.25	period 4/2 4/7	4/ 7	88	4.5	0.12	Menstrual
4/10	86	4.6	0.19		4/10	92	5.0	0.15	period 4/7 4/11
4/14	96	4.9	0.13		4/14	85	4.3	0.16	
4/17	92	5.0	0.20		4/17	90	4.5	0.08	
4/21	89	4.7	0.26		4/21	84	4.7	0.18	
4/24	90	4.5	0.15		4/24	90	4.7	0.26	

COMMENT

From a study of the data presented, it is understood why the reports in the literature are so confusing. The results are far from consistent, and there are no definite variations in the hemoglobin and red blood cells associated with menstruation. The coincident changes in the reticulocyte percentage support this statement. If there were a regular and significant drop in the red count during menstruation, there should have been a definite postmenstrual reticulocyte peak, indicating regenerative activity in the bone marrow. No such peak occurs, and the percentage of reticulocytes varies during the different phases of the menstrual cycle merely within the limits of error of the method. This indicates that the bone marrow is not called on to increase its regenerative activity. It therefore appears that in normal women the process of red cell regeneration is but slightly, if at all, influenced by the menstrual cycle.

SUMMARY

1 The process of red cell regeneration was studied in six relatively normal young women in relation to the menstrual cycle.

2 Studies of the hemoglobin and red blood cell counts made at biweekly intervals over a period of three months reveal no definite changes coincident with the various phases of menstruation.

3 The activity of the bone marrow as indicated by the reticulocyte count is not influenced by the menstrual cycle.

Book Reviews

Handbuch der inneren Medizin Herausgegeben von G. von Bergmann und R. Staehelin. Band VI. Nieren und Ableitende Harnwege. Die doppel-seitigen hamatogenen Nierenerkrankungen, von F. Volhard. Die ein- und beidseitig auftretenden Nierenkrankheiten (sogenannten chirurgische Nieren-affektionen). Blase, Prostata, Hoden und Nebenhoden, Samenblasen, funktionelle Sexualstörungen, von F. Suter. Second edition. Price. Teil 1, 98 marks, Teil 2, 99 60 marks. Pp 2137, with 298 illustrations. Berlin. Julius Springer, 1931.

The remarkable growth in the last two decades of the body of knowledge concerning Bright's disease is directly reflected in the evolution of the second edition of Volhard's great classic. From 673 pages of text in the 1918 volume, 1,722 pages, many in small type, have developed. A bibliography of about 20 pages in 1918 has increased to 152 pages in 1931. The literature is so thoroughly reviewed by extensive quotations and abstracts that an entire library is represented in these two books. Nothing of any significance has been left out. Add to this thoroughness a lucid, direct and pleasing style, perfect arrangement of the material, good typography and numerous excellent illustrations, and one has a permanent literary monument to Volhard's genius.

No attempt will be made to review more than a few aspects of the scientific contents, although every page is replete with interesting material. Volhard is a more confirmed "vital secretionist" than ever before, in spite of the recent work of Richards and his associates. He doubts the existence of glomerular filtration and even denies the occurrence of filtration in the choroid plexus. At times he allows the warm conviction of beautiful logic to overweigh the cold evidence of facts. He attacks Cushny's theory of urine formation on grounds somewhat antiquated at present. His arguments are always stimulating, however, and should provoke further investigation. There is an excellent discussion of the nerve supply of the kidney and of the problems of nervous regulation of renal function. The American work on renal function tests by Addis and Van Slyke and their associates is well presented. The author indulges in some clever juggling of Ambard's formulas to arrive at conclusions of rather doubtful objective value.

As to lymph formation and edema in general, Volhard vigorously supports the theory of active secretion by the vascular and lymphatic endothelium. In fact his credo is that the function of the capillaries is to regulate and inhibit mechanical filtration. Edema, therefore, is caused largely by increased permeability of the capillary wall on the basis of general damage of the tissues, a vague "dropsy of the tissue colloids". Renal edema is always extrarenal in origin, acute nephritic edema is cardiovascular, while chronic nephrotic edema is definitely attributed to albuminuria and hypalbuminemia, in view of the recent clinical and experimental data on this relationship.

It is to the problem of hypertension that Volhard has made his most important contributions. The "red" and "pale" types are distinguished on the basis of the mechanisms involved in their production. In the "pale" hypertensives (acute diffuse glomerulonephritis, "malignant" hypertension, eclampsia) there is a general arterial spasm (also angiospastic neuroretinitis) due to the presence in the blood serum of directly pressor chemicals and substances that sensitize the arterioles to the normal epinephrine content of the blood. These substances perhaps originate in the kidney under conditions of local circulatory or metabolic derangement. The evidence for all this seems quite acceptable to Volhard. Confirmation of the facts is urgently indicated. As to "red" hypertension, the only unquestionable etiologic factor is age. The author's attempt to explain essential hypertension on unproved physical changes in the small arteries will probably not satisfy most investigators in this field, but the distinction made between active contraction of arterioles and passive resistance to distention may represent a germ of the truth. One thing is certain, as Volhard states. Every persistent hypertension is in close relation

to the kidney, being either the result or the cause of a renal disease. The cerebral vascular disturbances so common in hypertension are dealt with along the lines of recent work on functional vascular disease. Albuminuric retinitis is termed "angiospastic retinitis" and correlated with the chemical pressor agents responsible for hypertension.

After an excellent historical review, Volhard dismisses physiologic, symptomatic and histologic classifications of renal disease and makes a powerful plea for the now famous "pathogenetic system." Opposing points of view are freely discussed, at times in a charmingly personal vein. How "ischemia" and "angiospasm" displaced "inflammation" in Volhard's thoughts on glomerulonephritis and the "combination form" ("malignant nephrosclerosis") is dramatically portrayed in this and in later sections of the text. The author naively laments the original lack of interest in his "discovery" on the part of prominent pathologists and clinicians. Recently, however, there has been adequate recognition. Whether Volhard is right or wrong, his point of view on the histogenesis of glomerular and vascular lesions has been a potent ferment and will continue to stimulate inquiry into fundamental problems of the pathologic physiology of the vascular system.

In the second volume, the clinical aspects of Bright's diseases are thoroughly covered, numerous and detailed case reports being included. Chronic nephrosis is not considered as a primary metabolic disease, but the whole nephrotic syndrome is attributed to loss of normal serum protein in the urine. As to why slight glomerular changes are associated with most severe albuminuria, is a mystery. Volhard says decisively "Genug, das Nephritis-Nephrose-Problem ist heute ungeklarter denn je" (Amen). A systolic blood pressure level above 120 mm of mercury always rules out pure nephrosis, but a lower figure does not justify a diagnosis of "nephrosis," because patients with proved diffuse glomerulonephritis may have low blood pressures for a long time. In short and in truth, "die Diagnose einer echten Lipoidnephrose" is also "keine leichte Aufgabe."

Volhard does not believe that a true diffuse nephritis has ever been produced in animals. The essence of chronic nephritis is seen in the persistence or occurrence of general and renal vasoconstriction. The varying clinical forms of the disease depend on the balance between circulatory disturbance and restitution. Even in chronic nephritis there is a long period of functional vascular trouble. As to treatment, von Noorden's advice to the physician is given. Forbid as little, instead of as much, as possible. Allen's rigid salt-free diet is enthusiastically recommended for patients with hypertension. Volhard is skeptical about the effects of most of the so-called vasodilators. His clinical subdivision of hypertension is rather complex and confusing, but the author makes a heroic attempt to mix functional and organic renal vascular changes in the proper proportions to explain various difficult problems.

The arrangement of the subject matter in the part by Suter follows the plan of the first edition. There are general sections that deal briefly with the symptomatology and methods of diagnosis of urological conditions. The special sections take up systematically the congenital malformations of the urinary tract, the various infections, calculous disease, obstructive syndromes, tumors, cystic conditions, inflammations of the perirenal fat, renal vascular accidents, diseases of the bladder, prostate, testes and seminal vesicles and functional disturbances of the male genital organs. The recent advances in the diagnosis and treatment for surgical diseases of the urinary tract are well covered in this edition. The author presents conflicting theories and practices in an objective manner. The illustrations are well chosen, and the bibliography is satisfactory. This section of the "Handbuch" should prove to be a valuable source of reference to both urologists and internists. It must be pointed out, however, that details of surgical technic do not come within the province of the text.

THE BIOLOGIC VALUE, IODINE CONTENT, HISTOLOGIC STRUCTURAL AND CLINICAL PICTURE OF GOITER *

A JORDI, M D

Edith Claypole Memorial Research Fellow, 1928-1930

BERN, SWITZERLAND

In 1916, Graham ¹ applied the Gudernatsch test to goitrous material of various kinds and showed that a certain definite relationship exists between the iodine and colloid content and the physiologic activity of tadpoles on which the test is made. Since then a great number of similar experiments have been carried out in different countries on every kind of goiter. Particular reference might be made to the work of Wegelin and I. Abelin,² of C. Abelin,³ and of Branovačky ⁴ on normal and abnormal human thyroid glands of all clinical and histologic groups, of Wydler ⁵ and of Dubois ⁶ on the goiters of cretins, and of Branovačky and Pelech ⁷ on certain malignant goiters. In 1923, Hara ⁸ applied the Asher-Streuli test on rats to different types of goiter.

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* From the George Williams Hooper Foundation and the Department of Bacteriology, University of California, San Francisco

* The results were partly reported at the annual meeting of the American Association for the Study of Goiter, at Seattle, July 10-12, 1930

1 Graham, A. A Study of the Physiological Activity of Adenomata of the Thyroid Gland, in Their Relation to Their Iodine Content as Evidenced by Feeding Experiments on Tadpoles, *J Exper Med* **24** 345, 1916

2 Wegelin, C, and Abelin, I. Ueber die Wirksamkeit der menschlichen Schilddrüse im Froschlarvenversuch, *Arch f exper Path u Pharmakol* **89** 219, 1921, Weitere Untersuchungen ueber die Wirksamkeit menschlicher Kropfe im Kaulquappenversuch, *ibid* **105** 137, 1924

3 Abelin, C. Ueber den Jodgehalt von Kropfen im Vergleich zu ihrer histologischen Struktur und ihrer Wirkung im Kaulquappenversuch, *Arch f exper Path u Pharmakol* **124** 1, 1927

4 Branovačky, M. Die biologische Wirksamkeit verschiedener Kropfarten im Kaulquappenversuch, *Mitt a d Grenzgeb d Med u Chir* **39** 563, 1926

5 Wydler, A. Die Histologie der Kretinenstruma, mit Beruecksichtigung der Klinik des Kretinismus und der funktionellen Untersuchung, *Mitt a d Grenzgeb d Med u Chir* **39** 467, 1926

6 Dubois, M. Vergleichende Untersuchungen ueber den biologischen Wert des Kretinenkropfs, *Mitt a d Grenzgeb d Med u Chir* **39** 543, 1926

7 Branovačky and Pelech. Ueber den funktionellen Wert der Langhansschen wuchernden Struma, *Mitt a d Grenzgeb d Med u Chir* **39** 609, 1926

8 Hara, Y. Untersuchungen ueber die pathologische Physiologie des Kropfes mittels der Asher'schen Methode der Empfindlichkeit der Ratten gegen Sauerstoffmangel, *Mitt a d Grenzgeb d Med u Chir* **36** 537, 1923

His findings were confirmed and extended by Branovačky.⁹ The conclusions drawn from those investigations of the Bern school were that only within one of the different well defined clinicopathologic groups of goiter does there exist the relationship found by Graham—that goiters with high iodine and colloid content are as a rule more active than those with little colloid and low iodine content. For instance, in endemic clinically indifferent goiter, the biologic value decreases as follows: diffuse colloid, nodular colloid, diffuse parenchymatous and nodular parenchymatous goiter. These investigators furthermore showed that the biologic value decreases from the goiter in Graves' disease to the goiter in endemic cretinism thus: struma basedowiana, endemic, clinically indifferent goiter and goiter of cretins. The physiologic activity, therefore, does not depend on the quantity of the colloid, and at the present time no chemicohistologic or tinctorial method exists to distinguish, for instance, the colloid of a goiter of a cretin from that of a normally functioning diffuse colloid goiter. Only biologic methods can reveal greater differences between the different groups and reveal finer distinctions between goiters of the same group.

In 1928, Spatz¹⁰ published similar investigations on the Bavarian goiter which as a whole are in agreement with those of the earlier authors. During the same year, Williamson, Pearse and Cunningham¹¹ reported experiments on tadpoles with material from various types of goiter. Their results will be discussed later in connection with my findings.

The importance of regional factors that influence the growth and the histologic structure of goiter has been stressed by a great number of authors. The differences are so great that the question arose whether "goiter" is the same in different localities. This doubt, and the question whether a principal biologic difference exists between the diffuse primary exophthalmic goiter and the adenoma with hyperfunction, were the reasons why the experiments reported here were made.

Twenty-nine goiters (seven clinically indifferent adenomas, ten adenomas with hyperfunction, ten diffuse goiters of primary Basedow's disease, one goiter with hypofunction and one normal gland with a few nodules) were examined. The Gudernatsch test on tadpoles was made in all twenty-eight cases; the iodine determinations in twenty-seven and the Asher-Stiehl test on rats in thirteen cases.

9 Branovačky, M. Der physiologische Wert der verschiedenen Kropfformen unter gleichzeitiger Berücksichtigung des biologischen Experimentes und des Jodgehaltes. *Mitt. d. Grenzgeb. d. Med. u. Chir.* **37**: 488, 1924.

10 Spatz, H. Vergleichende klinische, histologische und biologische Studien am Münchener Kropfmateriel. *Deutsches Arch. f. klin. Med.* **158**: 257, 1928.

11 Williamson, G. S., Pearse, I. H. and Cunningham, H. M. The Two Products of Thyroid Activity. *J. Path. & Bact.* **31**: 254, 1928.

HISTOLOGIC CLASSIFICATION

Wegelin's¹² classification, the introduction of which was recommended by Marine,¹³ is used with slight alterations taken from the classification of Aschoff and Buerkle-de la Camp¹⁴ which is very similar. In order to avoid any misunderstanding, the main points are given here.

I *Struma diffusa*1 *Struma diffusa colloidis (macrofollicularis)*

(a) *Non proliferans* (stationary type, with enlarged, evenly round follicles)

(b) *Proliferans* (proliferating type with numerous "Sanderson'schen Polstern" i. e., epithelial intrafollicular proliferations)

(c) *Basedowifacata* (islets of "hyperplasia" between the follicles)

2 *Struma diffusa basedowiana*II *Struma nodosa (adenoma)*1 *Struma nodosa parenchymatosa*

(a) *Struma nodosa trabecularis*

(b) *Struma nodosa tubularis*

(c) *Struma nodosa microfollicularis* (majority of follicles less than 75 microns in diameter)

2 *Struma nodosa colloidis*

(majority of follicles more than 75 microns in diameter)

(a) *Struma nodosa colloidis non proliferans*

(b) *Struma nodosa colloidis proliferans*

(c) *Struma nodosa colloidis basedowifacata*

III *Struma diffusa combined with struma nodosa*

The chief possibility for misunderstanding lies in the fact that Wegelin considered nodule and adenoma synonymously, a point as yet still questioned by other authors. Wegelin based his conception on the fact that nodules show the main characteristic of adenomas, i. e., new growths, namely, the autonomy of growth, and on the fact that they grow from within, often destroying normal tissue by compression. He pointed out that the classification is empiric and that many transitional forms exist that are difficult to identify. This is especially true in the early stages of adenoma formation as different stages often occur in the same gland.

12 Wegelin, C. *Schilddruese* in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8.

13 Marine, D. The Essential Thyroid Changes in Goiter, *Arch. Path.* **10** 164 (July) 1930.

14 Buerkle-de la Camp. Einteilung der strumoesen Erkrankungen der Schilddruese von pathologisch-anatomischen Gesichtspunkten aus unter Beruecksichtigung ihrer klinischen Erscheinungen, *Arch. f. klin. Chir.* **130** 207 1924.

METHODS

The material was received shortly after the operation. Size, weight and macroscopic appearance were noted. Small pieces were cut out for histologic examination from different parts in order to obtain a complete picture of the structure. The material, fixed in physiologic solution of sodium chloride, three parts, and formaldehyde 40 per cent, U S P, one part, was embedded in paraffin and the sections were stained with hematoxylin and eosin and after the method of van Gieson. The results of the histologic examination were compared with those obtained at the department of pathology, University of California Hospital, and proved to be in agreement with each other. The goitrous material was chopped. Extreme care was taken to eliminate in adenomas all calcified and fibrous tissue, hemorrhages and adherent normal tissue. Thus only the active parenchyma was used for the experiments and the iodine determinations. The material was then dried and ground to an extremely fine powder and kept in sterile bottles. It is of decided advantage to work with dried material (independence of time, possibility of repeating experiments, accurate dosage, etc.)

The iodine determinations were made by Mr J B Dalton, of the department of biochemistry, University of California. Kendall's method in the modification of Kelly and Husband¹⁵ was used.

The tests on the tadpoles were carried out in August, September and October, 1929, and from April to the beginning of September, 1930. Second year tadpoles of the species *Rana catesbeiana* were used exclusively. This large species, measuring from 110 to 155 mm in length, has many advantages, since it is much easier to follow the details of the metamorphosis and to obtain exact measurements. As this species completes metamorphosis in two years, a full scale of effects can be obtained by feeding goiters of different activity. The normal controls metamorphose so slowly that differences in animals fed with material of very low physiologic activity can be detected. Thus no goiter was found that failed to influence the metamorphosis. Preliminary experiments showed that the animals were much more sensitive to the active substances when the metamorphosis had already started, which is in agreement with the experiments made by different authors (Wegelin and Abelin, Branovačky, Dubois and others). Therefore only animals with hind-legs of from 12 to 16 mm in length were used. Eight series of experiments were made, each including from three to six goiters and two controls. The animals used in one series were all from the same locality and had therefore lived under the same conditions. In two cases in which outstanding results were obtained the experiment was repeated with satisfactory conformity. Four animals were used for each goiter and the same number for each control. The animals were kept in glass tanks containing 2,000 cc of city tap water in the middle of a well lighted room but were not exposed to direct sunlight. The water was changed every day, and to avoid changes of temperature only water that had been kept for twenty-four hours in the same room was used. All the other precautions outlined by Branovačky⁴ were taken. The animals were fed every other day with 0.2 Gm of the desiccated material. Every other day one control received three tablets of 5 grains of "Tabloid Thyroid Gland, Burroughs and Wellcome" and the other control dried liver. All the animals were fed with finely cut fresh lettuce on alternate days. Three tablets of 5 grains represent 0.972 Gm, or approximately 1 Gm of fresh gland. Since on an average the dry material equals one fifth of

15 Kelly and Husband. *Biochem J* 18 951, 1924

the weight of the fresh gland or goiter, 1 Gm of normal standardized thyroid gland as contained in three tablets is equivalent to 0.2 Gm desiccated goiter material

All results were compared with the effect obtained by this highly standardized product. Thus all the factors that might influence the course of the metamorphosis, such as different season, different temperature and different local origin of the animals, were eliminated. Each day's food was left in the tanks fully twenty-four hours. As the temperature in San Francisco is relatively low during the summer months (rarely 80 F), fermentation almost never occurred. The animals were fed with the same amount of desiccated material until they died. Measurements (total length, width, length of legs and tail, width of mouth) were taken at the beginning of the experiments, then twice a week thereafter, and just before fixing the animals in Bouin's fluid. The course of the metamorphosis such as appearance of "violin-shape" (Geigenform), loss of the horny jaws and the appearance of the forelegs was recorded daily. At the end of the experiments photographic pictures of the tadpoles were made.

EVALUATION OF THE RESULTS

Since the metamorphosis takes a much longer time with *Rana catesbiana*, unfortunately the scheme of Brianovačky⁴ cannot be applied. Instead, diagrams like those shown were made in each case demonstrating clearly the course of the metamorphosis. The curve, which is obtained by subtracting the average length of the hind legs from the average length of the tails, is especially characteristic as it correlates both factors, the influence on the growth of the legs and on the reduction of the tail. The difference in the activity of the various specimens could thus be estimated as early as at the time of the third measurement. Unfortunately, for lack of space, it is impossible to publish all the diagrams. But they revealed, in agreement with the results of the earlier workers, that the average time of death is in a constant relationship to the course of the metamorphosis, as evidenced by the character of the curve, by the average time of the appearance of "violin-shape" and forelegs and by the average time of the loss of the horny jaws. As the effect of the standard product of Burroughs and Wellcome varied in different series due to seasonal and other factors, a correction had to be made. This was done by subtracting the average time of death of these animals from the average time of death of the animals fed with goiter material. Thus for goiters that were more active than the thyroid substance I used a minus sign and for those that were less active, a plus sign. This gives a rather accurate picture of the degree of the effect on the tadpoles.

THE ASHER-STREULI TEST ON RAIS

The Asher-Streuli test is based on the fact that rats after having been given injections of, or fed with, thyroid substances become more sensitive to a deficiency of oxygen produced by evacuation. This

increase of sensitiveness is in a constant relation to the quantity and the physiologic value of the fed material. Details are given by Duran,¹⁶ Asher and Streuli,¹⁷ Hara,⁸ Branovačky,⁹ and de Quervain.¹⁸

The method outlined by Branovačky⁹ and not the original one by Hara⁸ was mainly followed. Only full grown rats were used for the tests. The average of the four typical reactions (excitement, dyspnea half lying [halbe Bauchlage] supine [schlafte Bauchlage]) were determined before and after the feeding, using from twenty-three to twenty-four minutes for evacuation. The course of the evacuation was always strictly the same: from two to three minutes to 660 mm of mercury and then four minutes for each following 100 mm. The average reaction of the normal animal was found greater with 300 mm than in the animals used by Branovačky, the maximum and minimum being 318 and 286 mm. Death occurred frequently below 180 mm. The evacuation was discontinued at this pressure and not at 160 mm as in Branovačky's experiments. Normal atmospheric pressure was reestablished in one and one-half minutes. There was not enough material left from the tadpole experiments for the rat tests in all cases. Only thirteen cases were tested, and a different method of feeding had to be worked out. Since all the manifestations of the administration of thyroid substances appear only after a certain latent period, the time of feeding was prolonged to six instead of three days, and the animals were tested on the seventh day. Thus a higher effect was reached with the same amount of material than when fed during a shorter time. Two-tenths grams of dried goiter material was suspended in 10 cc physiologic solution of sodium chloride and fed every day by means of a stomach tube. The total amount was therefore 1.2 Gm. One control received three tablets of 5 grains (0.32 Gm) each of thyroid substance (Burroughs and Wellcome) daily for the same number of days. All tests were made as "blind tests" in order to eliminate any autosuggestion. Neither the clinical and histologic diagnoses nor the effect on tadpoles were known to me at the time the tests were made.

It is clear that the results are immediately comparable among themselves but not with those of the other authors. The values obtained

16 Duran, M. Das Verhalten von normalen, mit Schilddruesensubstanz getuetterten und schilddruesenlosen Ratten gegen reinen Sauerstoffmangel, *Biochem Ztschr* **106** 254, 1920.

17 Streuli, H. Das Verhalten von schilddruesenlosen, milzlosen, schilddruesen- und milzlosen Tieren bei O₂ — Mangel, zugleich ein Beitrag zur Theorie der Bergkrankheit, *Biochem Ztschr* **87** 359, 1918.

18 de Quervain, F. Goitre, London: J. Bale Sons & Danielssen, Ltd., 1924, Rueck- und Ausblicke in der Schilddruesen-Pathologie. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **39** 415, 1926.

are somewhat lower than those of Bianovačky. Instead of applying his evaluation of one plus for each 40 mm, the increase of reaction in millimeters of mercury is given in the charts. The accuracy of the method is about ± 20 mm.

I GOITER WITH HYPOFUNCTION

CASE 33—G. P., a housewife, aged 30, lived in California all her life (0-17 Sierra Nevada, goiter region, 17-30 in San Francisco). She had a goiter of six months' (?) duration. She showed symptoms of hypofunction such as nervousness, hot flushes, dry skin and loss of hair. The basal metabolic rate was minus 19 per cent.

The removed tissue weighed 40 Gm and consisted of two pieces, 5.5 by 4 by 2 and 6 by 3.5 by 2 cm. The cut surface showed a number of small colloid nodules. The surrounding tissue also showed an increase in colloid content. In this case the nodules were not separated from the other tissue, as the capsules were very thin.

Microscopic examination of the adenomas showed large follicles with moderately deep staining colloid and flat nonproliferating epithelium. Hemorrhage was present in some places. The fibrous tissue was increased in some of the nodules. The surrounding thyroid tissue showed large to very large follicles, with medium staining colloid and flat epithelium.

The histologic diagnosis was *struma diffusa colloides et nodosa colloides macrofollicularis nonproliferans*.

The tests showed

Iodine content, 0.148 per cent of dry substance

Effect on the tadpoles, medium (no. 33 in fig. 12)

Effect on the rat, + 38 mm. of mercury

The deviation in the results of the two tests is very striking in this case. In the Gudernatsch test the gland was more active than all the clinically indifferent and all the slightly hyperactive adenomas, but the figure obtained in the Asher-Streuli test was the lowest of all the goiters. Again it must be emphasized that the latter was done as a "blind test." Since in the Asher-Streuli test the influence of the thyroid substances on the gaseous exchange of the rat is measured, the low figure of plus 38 mm. would correspond with the low basal metabolism rate of minus 19 per cent. It is impossible to explain findings like this merely by a lack of thyroxin. The assumption of Oswald, de Quervain, Asher and other authors that the thyroxin is not the only product of secretion of the thyroid gland would seem indicated unless one assumes that the quality of the thyroxin is changed.

II CLINICALLY INDIFFERENT ADENOMAS

CASE 1—H. G., a housewife, aged 23, lived in England 0-1, in Canada 1-17 and since in San Francisco. She first noticed the goiter from five to eight years before the operation, and about one year before it started to grow rapidly. No symptoms of hyperfunction were present.

The removed tissue weighed 30 Gm and consisted of two adenomas, one 4 by 3 by 2.5 cm, the other 1 cm in diameter, which were joined together by some fibrous tissue. Some compressed thyroid tissue was adherent. The cut surfaces of the adenomas showed old and new hemorrhages and calcifications.

Microscopic examination showed that in most of the sections the adenomas contained small follicles, filled with medium staining colloid and lined by flat epithelium. The fibrous tissue was considerably increased throughout the tumor. In some areas the follicles were medium in size, and were filled with medium staining colloid. Here the epithelium was also flat and proliferated in places. In many follicles the signs of old and recent hemorrhage and collections of lymphocytes were present.

The histologic diagnosis was *struma nodosa parenchymatosa microfollicularis et nodosa colloides macrofollicularis partim proliferans*.

The test showed

Iodine content, not determined

Effect on the tadpoles, little

Effect on the rat, not determined

CASE 3—K. P., a man, aged 58, lived in Canada 0-15, in Ohio 15-34 and for the last twenty-four years in San Francisco. He first noticed his goiter about five years before the operation. From three to four years afterward he noticed symptoms suggestive of hyperfunction such as nervousness, irritability, feeling of warmth and increased appetite. These symptoms subsided from three to four months previous to the operation. The patient suffered from generalized arteriosclerosis (blood pressure 230 systolic and 110 diastolic) and chronic nephritis. He was treated with potassium iodide (quantity unknown) some time before the operation.

The removed tissue consisted of one immense, single, well encapsulated adenoma weighing 184 Gm and measuring 9 by 7 by 6 cm. The cut surface showed one cyst, 2 cm in diameter, with rather recent hemorrhage. The tissue was yellowish gray.

Microscopic examination of the specimen did not show normal thyroid follicles. In many parts the epithelium formed closely packed sheets, in other parts typical trabeculae separated by hyaline fibrous tissue and capillary vessels. The whole adenoma was well vascularized. In many parts the vessels were considerably distended. The parenchyma cells showed a rather pale staining, round nucleus.

The histologic diagnosis was *struma nodosa parenchymatosa partim trabecularis*.

The tests showed

Iodine content, 0.0390 per cent of dry substance

Effect on the tadpoles, very little (no 3, fig 11)

Effect on rat + 60 mm of mercury (average of three determinations)

CASE 4—L. N., a housewife, aged 43, lived in San Francisco during the last thirteen years. She had a goiter of twelve years' duration which increased rapidly during pregnancies. No definite symptoms of hyperfunction were present. The patient showed slight nervousness and slight tremor, also moderate tachycardia which could be due to the beginning menopause. She gained about 48 pounds (21.8 Kg) during the last four or five years.

The removed tissue weighed 42 Gm and consisted of two large pieces 7 by 4 by 2 and 5 by 3 by 2 cm. The latter, a well encapsulated adenoma was used in the experiment.

Microscopic examination of the specimen showed that the follicles in many places were medium in size with medium to deeply staining colloid and flat epithelium with no signs of proliferation. In other parts the follicles were very small with dark staining colloid and flat epithelium. The fibrous tissue was greatly increased throughout the adenoma.

The histologic diagnosis was *struma nodosa macrotollicularis non proliferans et nodosa parenchymatosa microfollicularis*.

The tests showed

Iodine content, 0.0344 per cent of dry substance

Effect on the tadpoles, very slight, atypical (no 4, fig 11)

Effect on the rat, not determined

CASE 6—D. R., a high school student, aged 19, lived in an endemic goiter region all his life. The goiter started to grow eleven years before the operation, gradually increasing in size. The patient had had a feeling of pressure and slight dyspnea at times, but no other symptoms.

The removed tissue weighed 197 Gm., and consisted of two large masses and some smaller adenomas, 12.5 by 6 by 4.5 and 9 by 5.5 by 4 cm. The larger pieces were lobulated in three parts. One proved to be a cyst filled with blood, but the other was of firm consistency with a rather uniform cut surface. Some new and old hemorrhages as well as calcifications were present. The smaller adenomas showed the same macroscopic picture.

Microscopic examination showed that the picture varied to a great extent. In some parts the follicles were large, with medium staining colloid and with flat to low nonproliferating epithelium. In other parts the epithelium of large follicles showed intensive proliferation. The papillae were so tall that the follicles resembled the uterine tube. In still other parts the follicles were very small with deeply staining colloid, embedded in rather wide, partly hyaline septums of fibrous tissue. New and old hemorrhage and calcifications were present throughout the sections.

The histologic diagnosis was *struma nodosa colloides macrotollicularis proliferans et nonproliferans et nodosa parenchymatosa microfollicularis, partim cystica*.

The tests showed

Iodine content, 0.0323 per cent of dry substance

Effect on the tadpole, minimal, atypical (no 6 in fig 11)

Effect on the rat, not determined

CASE 19—G. S., a housewife, aged 49, lived in Minnesota 0-23, in Portland, Ore., 23-33, and for the last sixteen years in California (bay region). The goiter developed after childbirth, twenty-five years before the operation. Symptoms of pressure were present but no symptoms of hyperfunction.

The removed tissue weighed 235 Gm., and consisted of three pieces, 12 by 9 by 6, 6 by 5 by 4 and 7 by 7 by 4 cm. The cut surfaces showed similar appearance: wide septums of fibrous tissue lobulate the adenomas, some of which proved to be cysts. The other ones were very rich in colloid.

Microscopic examination of the specimen showed that the great majority of the follicles were large to very large in size, filled with medium staining colloid and lined by flat epithelium. In some parts the epithelium showed proliferation, and in these regions smaller follicles with cuboidal epithelium and medium staining colloid were present. Old and new hemorrhage, considerable fibrosis and calcifications were present in many parts.

The histologic diagnosis was *struma nodosa colloides macrotollicularis partim proliferans* (fig 9).

The tests showed

Iodine content, 0.0372 per cent of dry substance

Effect on the tadpoles, very slight (no 19 in fig 11)

Effect on the rat, + 50 mm of mercury

CASE 24—P. C., a housewife, aged 68, lived in Sweden 0-12, in Chicago 12-22, and ever since in San Francisco. The duration of the goiter was five years. One year before the operation, the patient noticed symptoms of pressure and dyspnea. No symptoms of hyperfunction were present. The dry skin and loss of hair were probably due to senium and not to hypofunction of the thyroid gland.

The removed tissue weighed 75 Gm., and consisted of several small pieces. They were divided by coarse fibrous septums into large and small lobules varying in size from 0.5 to 3 cm.

Microscopic examination showed that the nodules were surrounded by wide tracts of fibrous tissue which contained mostly very large follicles filled with pale colloid and lined by flat to cuboidal epithelium. Proliferations were missing in many sections. In other parts they were predominant, forming papillae. Here small follicles were present.

The histologic diagnosis was *struma nodosa colloides macrofollicularis partim proliferans*.

The tests showed

Iodine content, 0.0501 per cent of dry substance

Effect on the tadpoles, medium (no 24 in fig 12)

Effect on the rat, not determined

CASE 25—H. N., a housewife, aged 55, lived in Illinois, Omaha and St. Louis, and during the last twenty-seven years in San Francisco. She first noticed her goiter thirty-five years before the operation. She was nervous for the last ten years. No signs of hyperfunction were present.

The removed tissue consisted of three large pieces, 6 by 6 by 4.5 and 7 by 5 by 4 and 4 by 2 by 1.5 cm. They were roughly encapsulated. The cut surfaces showed numerous nodules measuring from 0.5 to 1.5 cm in diameter. Hemorrhage, new and old, and calcifications were present. The first mentioned adenoma was used in the experiments. It weighed 65.5 Gm. Only 30 Gm of parenchyma were obtained.

Microscopic examination of some of the nodules showed medium to large sized follicles with medium to deeply staining colloid and flat nonproliferating epithelium. In others the follicles were small with little or no deeply staining colloid and flat epithelium. In many parts they were embedded in partly hyaline fibrous tissue. Lymph cell infiltrations were present in both types of nodules. Signs of hemorrhage were seen in both septums and follicles.

The histologic diagnosis was *struma nodosa colloides macrofollicularis non proliferans et nodosa parenchymatosa microfollicularis*.

The tests showed

Iodine content, 0.0411 per cent of dry substance

Effect on tadpoles, very slight (no 25 in fig 12)

Effect on rat, not determined

The iodine content was found to be lowest in this group. It varied between 0.0323 and 0.0501 per cent of dry substance. These figures are as a whole in agreement with the findings of other authors. It is,

of course, impossible to draw far reaching conclusions from a limited number of cases. However, deviations to both sides and notably small figures as in the goiters of Cleveland Bein (Switzerland) and Freiburg (Germany) were not found. Graham¹ found the iodine content in various types of adenomas in Cleveland (Ohio) from 0.0001 traces to 0.131 per cent, Schmitz-Moormann¹⁹ in adenomas in Freiburg (area of endemic goiter) from 0.0033 to 0.0848 per cent, and C. Abelin in the struma nodosa parenchymatosa from 0.0025 to 0.0846 and in the struma nodosa colloidales from 0.0012 to 0.055 per cent, in Bein.

The failure to find low figures for iodine in goiter in California can be explained by the well known fact that both normal and goitrous thyroid glands are richer in iodine in areas near the sea than in inland regions.

The biologic activity in this group was found to be lowest of the groups studied and in general was parallel to the iodine and colloid content. However, the specimen in case 3 with no colloid was about as active biologically as those in cases 19 and 25, which were both rich in colloid. Furthermore, case 3 proves that the biologically active substances are not only present in the colloid but also in the epithelium, which is in agreement with the findings of Wegelin and Abelin² but not with those of Williamson, Pease and Cunningham¹¹. All the adenomas, save that in case 24, induced metamorphosis only a little earlier than the liver fed to the animals of the control series (fig. 8). Although the iodine and colloid content was low, no goiter was found that was entirely inactive, as reported by Graham, Wegelin and Abelin and others. It is impossible to compare the results directly, for the feeding during the experiments reported here was continued for a long period and probably revealed smaller amounts of active substances than the methods used heretofore.

Case 6 is of special interest. The influence on the metamorphosis was atypical. Although the animals were fed during more than two months, the tails showed no reduction and the mouths of the tadpoles with the typical horny jaws were still present at the end of the experiments. Meanwhile the forelegs broke through, and all the legs showed considerable increase in length. This unequal action was present but less marked in case 4 in which the mouths of two animals metamorphosed in the normal way. Both adenomas were poor in colloid and in relative iodine content. Wegelin and Abelin²⁰ found the same unequal action in different degrees in goiters in Switzerland not only with adenomas but also with diffuse colloid goiters having for the

19 Schmitz-Moormann P. Zur Strumafrage Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39** 82, 1926.

20 Wegelin and Abelin (footnote 2, second reference).

locality, approximately normal relative iodine content. They interpret this anomaly as a proof of a dysfunction of certain goitrous thyroid glands. The secretion evidently is not only altered in its quantity but also in its quality.

III. NORMAL THYROID GLAND WITH A FEW COLLOID NODULES

Unfortunately, an absolutely normal gland was not available, but that in case 35 consisted mostly of normal tissue. The capsules of the nodules were so thin that they were not separated, but the whole mass was used for the experiments.

CASE 35—A. T., a man, aged 42, lived in Montana 0-23 and in the Pacific northwest 23-42. The duration of the goiter is not known. Nervousness was the only symptom that might suggest hyperfunction.

The removed tissue weighed 33 Gm., and consisted of two pieces 4.5 by 3.5 by 2 and 4 by 2.5 by 2 cm. The cut surface showed some small adenomas, from 5 to 12 mm. in diameter, in a normal gland. The follicles were not separated from the other tissue.

Microscopic examination of the small adenomas, separated by a thin capsule of fibrous tissue, showed large to very large follicles with medium staining colloid and flat nonproliferating tissue. In the surrounding tissue the follicles were medium to large, with medium staining colloid and flat epithelium.

The histologic diagnosis was a normal gland with a few nodules (*nodosa colloides macrofollicularis nonproliferans*).

The tests showed

Iodine content, 0.193 per cent of dry substance

Effect on the tadpoles, strong (no. 35 in fig. 12)

Effect on the rat, not determined

The iodine content can probably be considered about normal. The biologic activity of the mostly normal material was very high, but somewhat lower than the thyroid tablets (Burroughs and Wellcome) of the controls of the same series.

IV. ADENOMAS WITH SLIGHT OR QUESTIONABLE HYPERFUNCTION

CASE 23—S. J., a housewife, aged 34, lived in Arkansas and Oklahoma 0-25, and during the last nine years in California (Los Angeles and San Francisco). She first noticed her goiter about eight years before the operation. After six years, during a pregnancy, questionable symptoms of hyperthyroidism were present. Six months before the operation they became more definite, and immediately before the operation they were mild. They consisted of nervousness, insomnia, tachycardia (from 80 to 90), hyperhidrosis at times and slight tremor of the fingers.

The removed tissue weighed 83 Gm., and consisted of one major adenoma, measuring 7 by 4 by 2 cm., and several smaller ones. The cut surfaces showed mostly colloid tissue separated by wide septums of fibrous tissue. A few recent hemorrhages and some calcifications were present.

Microscopic examination of the specimen showed that in some parts the majority of the follicles were medium in size with flat epithelium, in many places proliferating, and filled with medium to deeply stained colloid. In other areas

the follicles were small with flat epithelium and mostly dark stained colloid. Wide septums of fibrous tissue separated the adenomas irregularly. Collections of lymphocytes were occasionally present near the septums. Signs of old and recent hemorrhage were seen in some of the larger follicles.

The histologic diagnosis was *struma nodosa colloides macrofollicularis proliferans et nodosa parenchymatosa microfollicularis* with hemorrhages, fibrosis and calcifications.

The tests showed

Iodine content, 0.0980 per cent of dry substance

Effect on the tadpoles, medium (no. 23 in fig. 12)

Effect on the rat, not determined

CASE 26—H. M., a housewife, aged 45, lived around the great lakes and in the state of Washington, and for the last few years in San Francisco. The duration of the goiter was thirty-three years, of the symptoms of hyperthyroidism, two years. The symptoms consisted of moderate nervousness, tachycardia (from 96 to 105), palpitation, tremor, perspiration and loss of weight (9 pounds [4.1 Kg.] during the last year).

The removed tissue, composed of two huge pieces measuring 10 by 8 by 3 cm. and 11 by 6 by 4 cm., consisted of different adenomas, showing varying degrees of degeneration. Some formed cysts, filled with brownish fluid, the others were mostly of the colloidal type, but some showed old and new hemorrhages, fibrosis and calcification.

Microscopic examination of the specimen showed that in some parts the majority of the follicles were very large, distended with flat epithelium, intermixed with small areas of small follicles and low cuboidal epithelium. Some of the large follicles were filled with blood. Collections of lymphocytes were frequent and of considerable size. Other parts showed wide septums of partly hyaline connective tissue. Here the majority of the follicles were small with flat epithelium and light colloid. Only a few areas showed low cuboidal epithelium.

The histologic diagnosis was *struma nodosa colloides macrofollicularis partim basedowifcata* with hemorrhages, calcifications and formation of fibrous tissue.

The tests showed

Iodine content, 0.0672 per cent of dry substance

Effect on the tadpoles, slight (no. 26 in fig. 12)

Effect on the rat, not determined

CASE 28—M. M., a widow, aged 67, a shopkeeper, lived in Missouri until 35 years of age, since then she lived in Stockton, Calif. Her goiter was of twenty years' duration. It grew rapidly during the last three years, and at the same time symptoms of hyperthyroidism developed. They were mild at the time of the operation and consisted of nervousness, palpitation, muscular weakness and diarrhea, but no tachycardia or exophthalmos.

The removed tissue weighed 53 Gm. and consisted of two major portions and some smaller adenomas. The first mentioned measured 6 by 4 by 3.5 and 4 by 2.5 by 3 cm. and were composed of different small adenomas.

Microscopic examination of the specimen showed that in some parts the follicles were of medium to large size with intensely stained colloid and low epithelium, mixed with areas of very small follicles with flat epithelium and medium to lightly stained colloid. In other parts all the follicles were small with flat epithelium, separated by hyaline fibrous tissue. Hemorrhage was present in both follicles and stroma.

The histologic diagnosis was struma nodosa macrofollicularis proliferans et nodosa parenchymatosa microfollicularis

The tests showed

Iodine content, 0.0675 per cent of dry substance

Effect on the tadpoles, medium (no 28 in fig 12)

Effect on the rat, not determined

CASE 31—M E, a housewife, aged 40, lived in California (Sacramento valley and San Francisco) all her life. The duration of the goiter was eighteen years. Slight symptoms of hyperthyroidism developed six months before the operation, such as nervousness, palpitation, tremor, tachycardia (90) and a basal metabolic rate of plus 45 per cent. No exophthalmos was present.

The removed tissue weighed 76 Gm, and consisted of one large, well encapsulated adenoma, measuring 6 by 5.5 by 4 cm and weighing 65 Gm, and two small pieces of normal tissue. The adenoma was used for the experiments.

Microscopic examination of the specimen showed small follicles with little or no colloid, lined by large cuboidal epithelium. The stroma was increased, faintly stained and edematous. The thyroid tissue was of normal structure.

The histologic diagnosis was struma nodosa parenchymatosa microfollicularis in a normal thyroid gland.

The tests showed

Iodine content, 0.0605 per cent of dry substance

Effect on the tadpoles, slight (no 31 in fig 12)

Effect on the rat, not determined

The iodine content in the latter four cases ranged between 0.0605 and 0.0980 per cent, which is higher than in the clinically indifferent adenomas. This is of great significance. Schmitz-Moormann¹⁹ showed that the relative iodine content of the normal gland steadily increases with the age of the patient and that frequently the same happens in adenomas. This would explain the fact that hyperthyroidism originating from these tumors appears only in later years, as Plummer²¹ and Boothby²² particularly point out.

The biologic activity on the average was higher than in the first group. However, one clinically indifferent adenoma, that in case 24 with 0.0501 per cent iodine, was considerably more active biologically than any of the goiters with slight hyperfunction. In order to explain this fact one has to take into account the degree of the function of the normal gland, the counteraction of the other glands with internal secretion and especially the individual sensitiveness of the autonomous nervous system factors which are all unknown.

There is no absolute relationship between the iodine content and the biologic activity. The specimen in case 23 with an iodine content of 0.098 per cent is even a little less active than that in case 28 with a

21 Plummer, H. S. The Function of the Thyroid Gland, Beaumont Lecture, Detroit Jan 27 1925.

22 Boothby, W. M. Adenoma of the Thyroid with Hyperthyroidism (Thyrotoxic Adenoma), Endocrinology 5 1, 1921.

content of 0.0675 per cent. Both, however, with high colloid content are more active than the specimen in case 31 with little colloid. Unfortunately, for lack of material, the tests on the rats could not be made in these cases.

The histologic picture does not show any notable characteristics.

V ADENOMAS WITH DEFINITE HYPERFUNCTION

CASE 10—D. P., a housewife, aged 40, lived in Italy 0-28, and in California (Sierra Nevada) 28-49. Her goiter was of twenty years' duration. During the last two years symptoms of hyperthyroidism developed such as a moderate degree of perspiration, tachycardia (from 90 to 100), tremor, recent loss of weight (20 pounds [9 Kg.] in three months), blood pressure 160 systolic 90 diastolic and thyrotoxic myocarditis. Five months before the operation she was treated with "medicine" that made her condition worse (probably iodine).

The removed tissue weighed 158 Gm., the two major pieces, measuring 9 by 6 by 2.5 and 7.5 by 5 by 2.5 cm., consisted of smaller and larger adenomas.

Microscopic examination of the specimen showed very large follicles with deeply staining colloid and flat epithelium, intermixed with areas of small follicles and tall cuboidal to columnar epithelium. Lymphocytic infiltration was not marked.

The histologic diagnosis was struma nodosa colloidescens basedowii.

The tests showed:

Iodine content, 0.147 per cent of dry substance.

Effect on the tadpoles, very strong, typical (no. 10 in fig. 12).

Effect on the rats, plus 98 mm. of mercury (average of three determinations).

CASE 17—M. B., a man, aged 62, always lived in Mendocino County, Calif. His goiter was of eighteen years' duration. Symptoms of hyperthyroidism developed six years before the operation with nervousness, palpitation, tremor, diarrhea and excessive perspiration. They were severe at the time of the operation. The patient lost weight (32 pounds [14.5 Kg.] during the last five years and 13 pounds [5.9 Kg.] during the last year) in spite of a good appetite. The heart showed auricular fibrillation (pulse from 110 to 120). The blood pressure was 180 systolic and 70 diastolic.

The removed tissue weighed 58 Gm., and consisted of two adenomas 4 by 3.5 by 2.5 and 5 by 4 by 3 cm.

Microscopic examination of the specimen showed very large follicles with medium staining colloid and low, partly desquamating epithelium. Adjacent were areas with small follicles lined by low cuboidal epithelium. New and old hemorrhages were scattered throughout the tissue, collections of lymphocytes were numerous. There was considerable formation of fibrous tissue. A small piece of thyroid tissue showed normal structure.

The histologic diagnosis was struma nodosa colloidescens basedowii in a normal gland (fig. 1).

The tests showed:

Iodine content, 0.249 per cent of dry substance.

Effect on the tadpoles, extremely strong, typical (no. 17 in fig. 12, diagram fig. 2).

Effect on the rat, + 174 mm. of mercury.

CASE 18—W. M., a housewife, aged 61, lived in San Francisco during the last few years. The duration of the goiter was not known. Symptoms of hyperthyroidism had been present for two years. The symptoms which were rather severe,

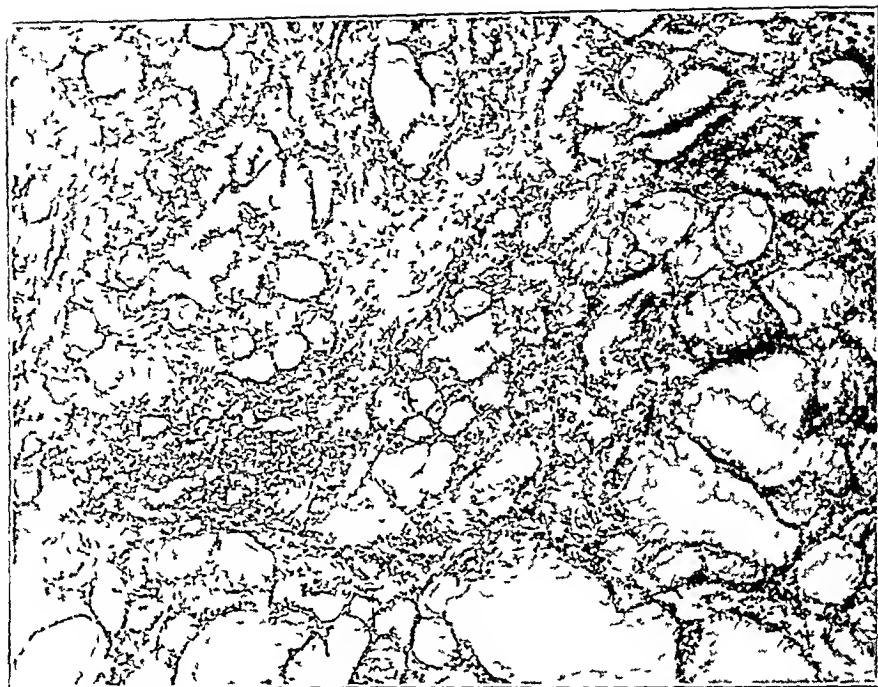


Fig 1 (case 17) —Struma nodosa colloides basedowificata In this section are seen medium large and small follicles, formation of papillae in some follicles at the left and collections of lymphocytes Hematoxylin and eosin, $\times 75$

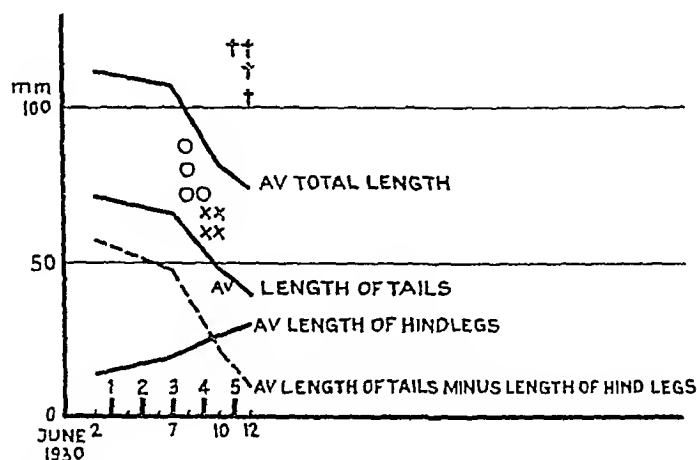


Fig 2 (case 17) —Effect on the metamorphosis of the tadpoles Maximum in the group in which adenomas with hyperfunction were used The iodine content was 0.249 per cent In this and in figures 4, 6, 7 and 8, the measurements, in millimeters, represent the average of the total length, the length of the tail, and the length of the hind legs of four tadpoles used for one specimen or for one control The last points on the curves demonstrate the average lengths at the average time of death The circle indicates the loss of horny jaws, \times , the appearance of the foreleg (l = left, r = right), and the dagger, the death of one animal

consisted of nervousness, palpitation, tremor, excessive perspiration, tachycardia (from 120 to 130), increased appetite, loss of weight (30 pounds [13.6 Kg] in one and one-half years), blood pressure 180 systolic, 70 diastolic, but no exophthalmos

The removed tissue weighed 43 Gm, and consisted of four well encapsulated adenomas, 4, 3, 2 and 0.5 cm in diameter

Microscopic examination of the specimen showed that the majority of the follicles were very large with flat epithelium, partly desquamated and light to dark staining colloid. Adjacent were areas with small follicles and tall cuboidal or columnar epithelium and faintly staining colloid. Collections of lymphocytes were infrequent

The histologic diagnosis was *struma nodosa colloides basedowificata*

The tests showed

Iodine content, 0.163 per cent of dry substance

Effect on tadpoles, very strong, typical (no 18 in fig 12)

Effect on rat, not determined

CASE 27—J. T., a man, aged 55, lived in New York and Connecticut, and for the last twenty-five years on the seashore of the San Francisco peninsula. He had a goiter of ten years' duration, with symptoms of hyperthyroidism for about one year. The symptoms, consisting of nervousness, palpitations, tremor, excessive perspiration, tachycardia (130 at times) due to thyrotoxic myocarditis with auricular fibrillation, increased appetite and diarrhea, were marked. The patient was treated with compound solution of iodine (10 drops, three times a day) during the three months preceding the operation.

The removed tissue weighed 378 Gm, and consisted of three large pieces, one 11.5 by 8 by 5 cm composed of many nodules varying in size from 0.2 to 4 cm. Many showed hemorrhages, new and old, and some calcification. One single adenoma measured 8 by 7 by 6 cm, and one piece 6 by 5 by 4.5 cm showed a structure similar to the first one. The two first mentioned were used in the experiments.

Microscopic examination of the specimen showed that in some sections the follicles were very large with flat, in many follicles proliferating, epithelium and medium stained colloid, mixed with areas of small follicles with cuboidal epithelium. Small collections of lymphocytes were frequent. Some distended follicles showed old and new hemorrhage and others desquamation of the epithelium. In other parts the size of the follicles was more uniform, from small to medium, with faintly staining colloid and flat epithelium. Wide septums of partly hyaline connective tissue, showing signs of old hemorrhage, and some calcifications were present. Lymphocytes were missing in these parts. The histologic diagnosis was *struma nodosa colloides partim basedowificata et nodosa parenchymatosa microfollicularis*.

The tests showed

Iodine content, 0.276 per cent of dry substance

Effect on tadpoles, extremely strong (no 27 in fig 12)

Effect on rat, + 149 mm of mercury

CASE 32—B. L., a housewife, aged 33, lived in North Dakota and Idaho. She came to San Francisco two years before the operation for a goiter of eighteen years' duration. It had remained the same size until three years before the operation when, after childbirth, it began to grow rapidly. At the same time symptoms of hyperthyroidism developed, consisting of nervousness, palpitation, excessive perspiration, moderate tachycardia, muscular weakness and loss of weight. No exophthalmos was present.



Fig 3 (case 9) —Struma diffusa basedowiana The colloid contents in many follicles is greatly increased, as a sequel of a three months' treatment with iodine Hematoxylin and eosin, $\times 75$

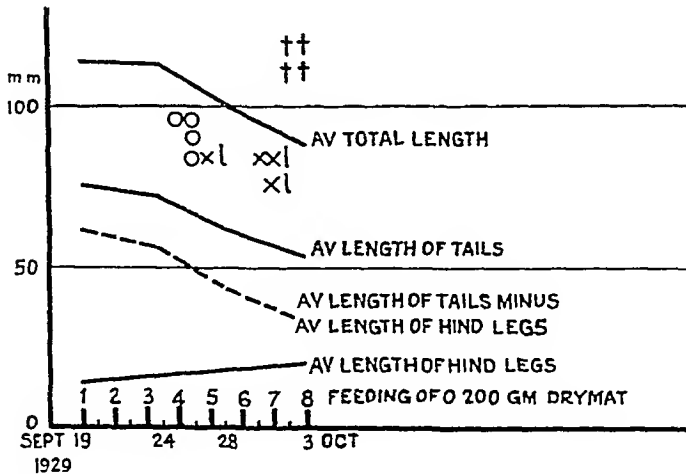


Fig 4 (case 9) —Effect on the metamorphosis of the tadpoles Maximum in the group in which struma diffusa basedowiana was used The iodine content was 0.560 per cent

The removed tissue weighed 65 Gm, and consisted of two large pieces 5.5 by 4 by 3 and 6 by 3 by 2.5 cm, formed by multiple colloid adenomas of different size. Some showed small calcifications.

Microscopic examination of the specimen showed enormously distended follicles with medium to lightly stained colloid lined by flat epithelium in many parts proliferating in a marked degree. Signs of old and new hemorrhage were present. Between the huge follicles were narrow areas with small follicles, lined by cuboidal epithelium. There were no collections of lymph cells present.

The histologic diagnosis was struma nodosa macrofollicularis proliferans.

The tests showed

Iodine content, 0.232 per cent of dry substance.

Effect on tadpoles, very strong (no. 32 in fig. 12).

Effect on rat, + 109 mm. of mercury.

CASE 34—M. L., a housewife, aged 40, an Armenian, lived in California for the last number of years. She had a goiter of eighteen years' duration which developed after childbirth. Symptoms of hyperthyroidism, consisting of nervousness, tremor, palpitation, excessive perspiration and tachycardia (from 120 to 130) had been present during the last two years. The basal metabolic rate was 20.4 per cent plus, one month before the operation.

The removed tissue weighed 78 Gm, and consisted of two pieces. One measured 5 by 4 by 2 cm and proved to be normal thyroid tissue. The other, weighing 60 Gm, was a single adenoma, well encapsulated, measuring 6.5 by 4.5 by 3 cm. Only this one was used for the experiments.

Microscopic examination of the thyroid tissue showed a normal structure consisting of medium sized lobules with small to medium large follicles. The colloid was well stained, and the epithelium was flat or low cuboidal. No areas of proliferation or collections of lymphocytes were found. The adenoma showed medium sized follicles with dark stained colloid and flat epithelium. Areas with small follicles were present, with flat to low cuboidal epithelium.

The histologic diagnosis was struma nodosa colloidis macrofollicularis partim proliferans in a thyroid gland of normal structure (fig. 10).

The tests showed

Iodine content, 0.204 per cent of dry substance.

Effect on the tadpoles, very strong (no. 34 in fig. 12).

Effect on the rat, + 124 mm. of mercury.

The relative iodine content varied between 0.147 and 0.276 with an average of 0.2118 per cent which is second highest of all the groups. The biologic activity, however, was higher in both tests. In case 17 the specimen showed the maximum of all the goiters examined (fig. 2) with the highest iodine content among the untreated (iodine) adenomas. The specimen in case 27 with an iodine content of 0.278 per cent, which had been treated with iodine, was somewhat less active about the same as the specimen in case 18 with an iodine content of only 0.163 per cent. A definite correlation between the iodine content and the biologic activity on the one hand, and the clinical activity on the other, was not present. However the goiter with the lowest iodine content and the lowest biologic activity was clinically moderately active while the goiter in case 17 with the highest biologic activity (fig. 2) was clinically very active. The two localities in which thyroid tablets were used for comparison in the

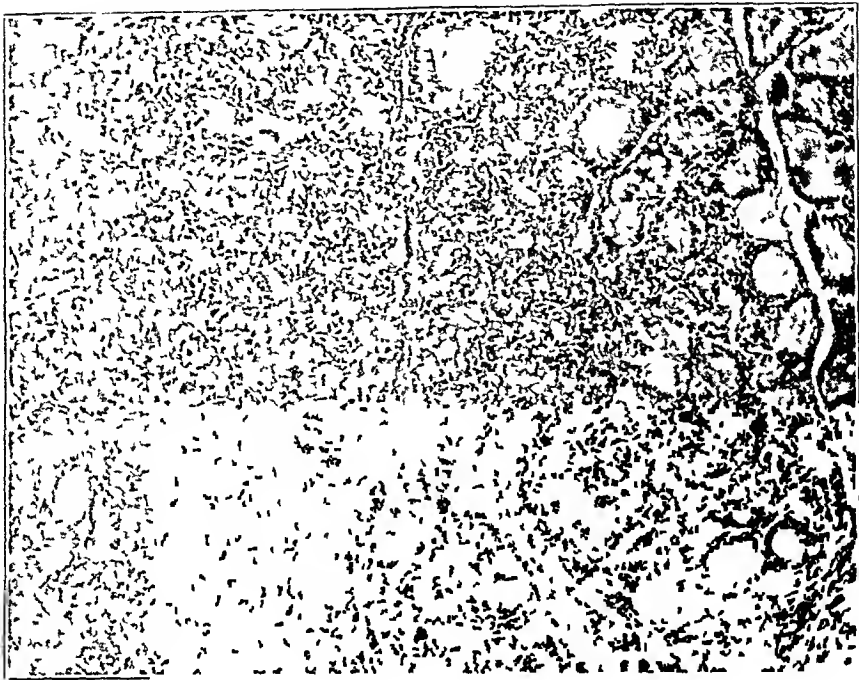


Fig 5 (case 14) —Struma diffusa parenchymatosa basedowiana Small follicles with little or no colloid are seen The duration of the treatment with iodine was nine days Hematoxylin and eosin, $\times 75$

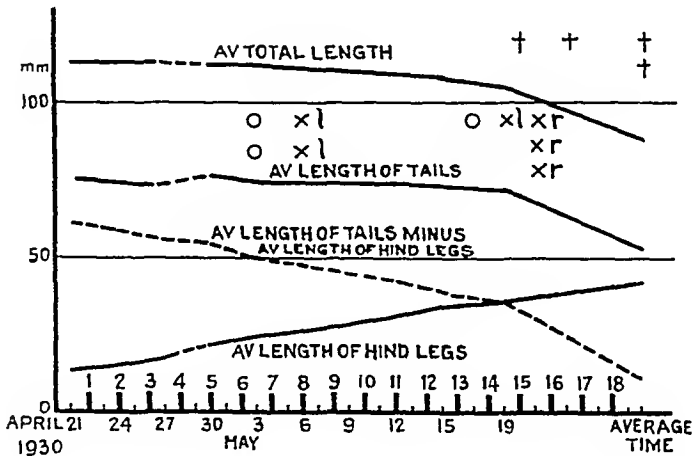


Fig 6 (case 14) —Effect on the metamorphosis of the tadpoles, very little In this group struma diffusa parenchymatosa basedowiana was used The iodine content was 0.196 per cent

Gudernatsch test, Bern and Munich are endemic centers. Although both primary and secondary Basedow's disease are much less frequent and milder in areas with endemic goiter than in other sections often enough cases with symptoms of extreme hyperactivity are observed. The most active adenoma of Brianovačky's¹ series, for instance, was from a patient with a basal metabolic rate of plus 52 per cent, the results from this case showed less biologic activity than the thyroid tablets (Parke, Davis and Company) with 0.2 per cent iodine. Some of the adenomas of the series of Spatz¹⁰ were clinically even more active, and in their effect on the tadpoles, as active as the "Thyroid-Dispert" used as standard. This would therefore suggest that in coastal areas adenomas with hyperfunction are biologically more active and clinically as active as those in inland areas. Further comparative studies on a larger scale will be needed to verify adaptation of the patients near the sea to a long-lasting hypersecretion.

The average iodine content of the adenomas in Brianovačky's series was only 0.0588 per cent, which is well below the iodine content of the normal glands in Bern. The six cases reported here revealed an average of 0.2118 per cent, which is probably as high as in normal glands near the sea, but is about four times as high as in the hyperactive adenomas in Bern.

It is of special interest to note that all the patients with the most active adenomas had lived on the coast for a number of years and that four of six specimens showed basedowification. One patient had been treated with large doses of iodine. The considerably higher colloid content of this group, as compared with the other adenomas is striking. However, the specimen in case 19 (fig. 9) was rich in colloid, but clinically indifferent and biologically of little activity. This indicates, in agreement with Wegelin and Abelin,²³ that the biologic value depends not on the quantity but on the quality of the colloid. A review of the material of a hundred operations, to be published elsewhere, showed, in agreement with other authors, the same fact, that the struma nodosa parenchymatosa and the colloides et parenchymatosa are clinically less active than the struma nodosa colloides proliferans et basedowificata.

VI. STRUMA DIFFUSA ET NODOSA WITH HYPERFUNCTION

CASE 15—N. C., a housewife, aged 47, lived in Utah until the age of 42, then in California (in one of the large valleys). She first noticed the symptoms of hyperthyroidism about sixteen months before operation. They became much worse four months after she had undergone an operation (gastro-enterostomy and hysterectomy). The symptoms at the time of the admission to the hospital were typical and moderately severe, consisting of nervousness, palpitation, tremor, hyperhidrosis, tachycardia (from 100 to 130), increased appetite, loss of weight.

²³ Wegelin and Abelin (footnote 2, second reference). Wegelin (foot

and exophthalmos. She was treated with compound solution of iodine for thirteen days before the operation ($\frac{1}{6}$ minim [0.01 cc] for two days, $\frac{1}{2}$ minim [0.03 cc] for three days and $\frac{1}{8}$ minim [0.0075 cc] for eight days) which relieved her symptoms somewhat.

The removed tissue weighed 72 Gm, and consisted of three pieces measuring 9.5 by 5.5 by 4.5 and 7 by 3.5 by 7.5 and 3.5 by 2 by 1.5 cm, respectively.

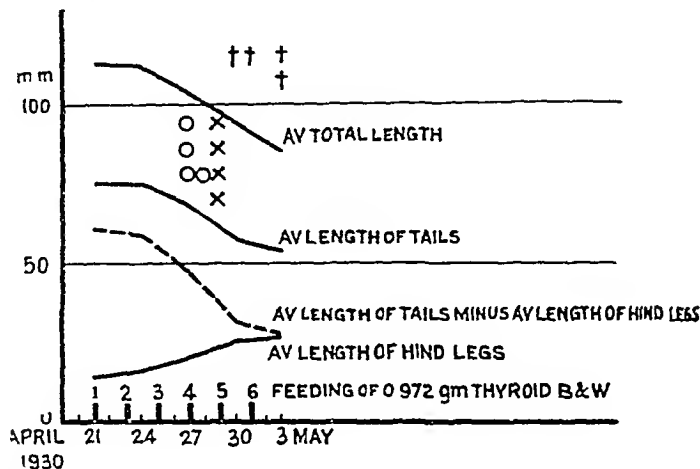


Fig 7 (control no 7) —Effect of thyroid tablets (Burroughs and Wellcome) on the metamorphosis of the tadpoles, very strong. The iodine content was 0.4 per cent.

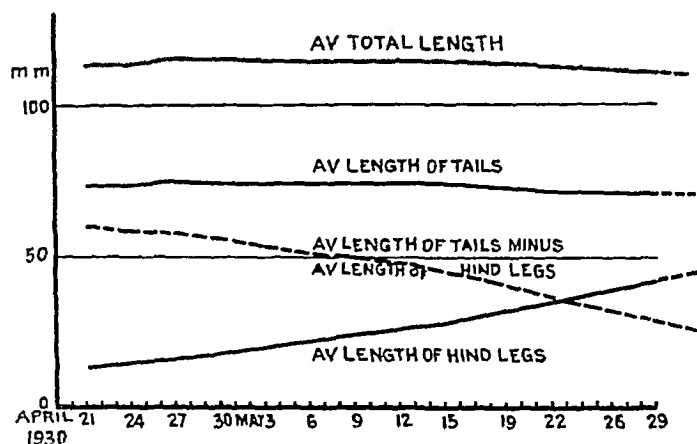


Fig 8 (control no 8) —Course of the metamorphosis of normal tadpoles, fed with liver and lettuce. At the end of the experiment all the animals are still alive, they still show the typical tadpole mouth with horny jaws. No forelegs have appeared.

Microscopic examination of the sections showed medium to large follicles with flat nonproliferating epithelium and medium staining colloid, intermixed with areas in which typical proliferations of the epithelium with cuboidal to low columnar cells were present. In still other areas the follicles were small with cuboidal to low columnar epithelium and lightly stained colloid. Collections of lymphocytes were infrequent and small. A few adenomas measuring from 1 to 1.5 cm were seen, the interior of which showed medium to large follicles with flat nonproliferating epithelium. In the periphery signs of typical basoidification were present.

The histologic diagnosis was *struma diffusa colloides basedowificata et nodosa colloides basedowificata*

The tests showed

Iodine content, 0.296 per cent of dry substance

Effect on the tadpoles, medium (no. 15 in fig. 11)

Effect on the rat, not determined

As the capsules of the adenomas in this specimen were very thin the whole mass was used in the experiments. The biologic activity was in spite of the high iodine content low compared with the typical goiters of Grave's disease. This might be due to the inferior biologic value of the adenomas in which the basedowification evidently started later.

VII DIFFUSE GOITERS OF PRIMARY BASEDOW'S DISEASE

CASE 2—W. M., a housewife, aged 29, had a goiter of two years' duration. The symptoms were of moderate degree, but typical, consisting of nervousness, palpitation, tremor, excessive perspiration, increased appetite, tachycardia (from 120 to 130) and exophthalmos. Stellwag, Moebius and Graefe's signs were positive. The patient was treated with the roentgen rays and compound solution of iodine one and one-half years before the operation. The goiter decreased in size, and the patient felt improved. Later the symptoms recurred. Compound solution of iodine was again taken intermittently for fourteen months, but was discontinued some time before the operation. One day before the operation, it was administered again.

The removed tissue weighed 12.5 Gm., and consisted of two pieces, measuring 4 by 2 by 1 and 2 by 2 by 0.8 cm.

Microscopic examination showed the gland to be divided by fibrous septums which were rather wide in places, into small to medium sized lobules. The follicles were small to medium in size, lined by high cuboidal to columnar epithelium. The colloid was mostly pale staining with vacuoles and serrated edges. Lymphocytic infiltration was marked.

The histologic diagnosis was *struma diffusa parenchymatosa basedowiana*.

The tests showed

Iodine content, not determined

Effect on the tadpoles, medium

Effect on the rat, not determined

CASE 5—R. E., an unmarried woman, aged 48, lived in California (bay region) all her life. She first noticed the symptoms six months before the operation. They were moderate, consisting of nervousness, palpitation, tremor, hyperhidrosis, tachycardia (from 100 to 110) and muscular weakness, but no ocular symptoms. The patient was treated with compound solution of iodine one month prior to the operation.

The removed tissue weighed 24 Gm. and consisted of two pieces 6 by 4 by 1.5 and 5 by 2.5 by 1.5 cm.

Microscopic examination showed medium to large follicles lined by flat to low cuboidal epithelium and filled with mostly deep staining colloid. Throughout the sections there were areas with very small follicles, containing little vacuolated colloid with desquamated epithelial cells. Here the epithelium was high cuboidal to columnar. Discrete areas of lymphocytes were rather infrequent.

The histologic diagnosis was *struma diffusa colloides et parenchymatosa basedowiana*.

The tests showed

Iodine content, 0.480 per cent of dry substance

Effect on the tadpoles, very strong (no 5 in fig 11)

Effect on rat, not determined

CASE 7—B. M., a housewife, aged 36, lived in Austria ("near Tyrol") up to the age of 19 and since then in California, on the coast. She had symptoms of Basedow's disease fourteen years before the operation, but she was better without medical treatment. The symptoms developed again ten months before operation, with nervousness, palpitation, tremor, excessive perspiration, tachycardia, increased appetite, muscular weakness and loss of weight (18 pounds [8.2 Kg.] in six months). The patient was treated with compound solution of iodine (10 drops three times a day) for three weeks preceding the operation. The

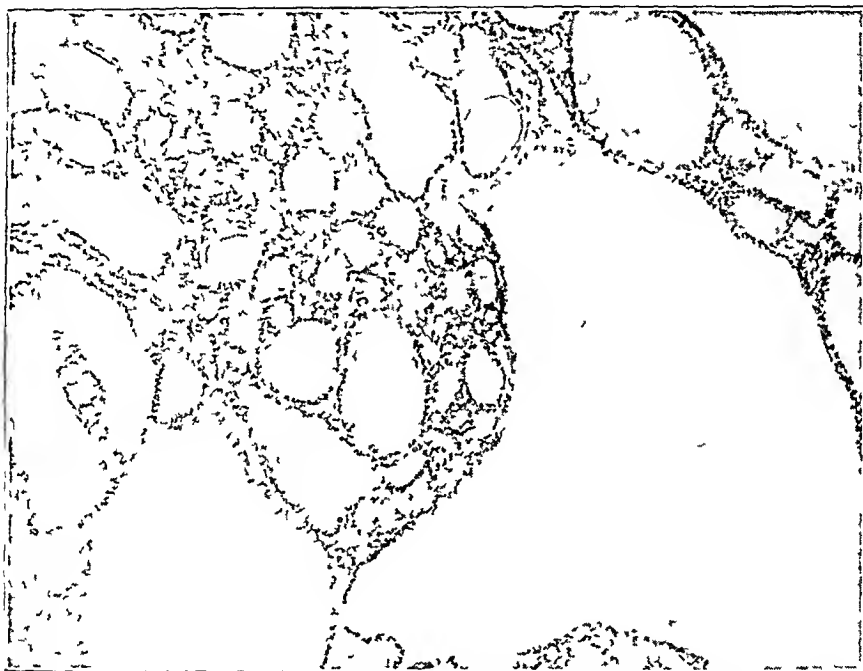


Fig 9 (case 19)—Struma nodosa colloides macrofollicularis, clinically indifferent. Van Gieson, $\times 75$

basal metabolic rate was 51 per cent plus before the administration of iodine and it dropped to 36 per cent plus after sixteen days of treatment. The other symptoms improved accordingly.

The removed tissue weighed 47 Gm., and consisted of two pieces 8 by 4 by 2.5 cm. and 5.5 by 2.5 by 1 cm.

Microscopic examination of the specimen showed that the follicles were mostly small with faint to medium staining colloid and chiefly cuboidal epithelium. Some follicles were of medium to fairly large size with flat epithelium. Areas of heavy lymphocytic infiltration were numerous.

The histologic diagnosis was struma diffusa basedowiana.

The tests showed

Iodine content, 0.246 per cent of dry substance

Effect on the tadpoles, medium (no 7 in fig 11)

Effect on rat $+ 108$ mm. of mercury

CASE 9—G F, a housewife, aged 46, always lived in California (bay region) The first symptoms of Basedow's disease developed four years before the operation The patient felt improved after a vacation and felt well for one year Two years before the operation, the symptoms again developed and became much worse after an attack of influenza eight months before They were typical but of a moderate degree, consisting of nervousness, palpitation, tachycardia and loss of weight (16 pounds [7.3 Kg]) The basal metabolic rate was 52 per cent plus three months before the operation The patient was treated from then until the time of the operation with compound solution of iodine (3 drops three times a day) and felt much improved She gained 5 pounds (2.3 Kg), and the tremor and the hyperhidrosis especially were less severe There was no exophthalmos at the time of the operation

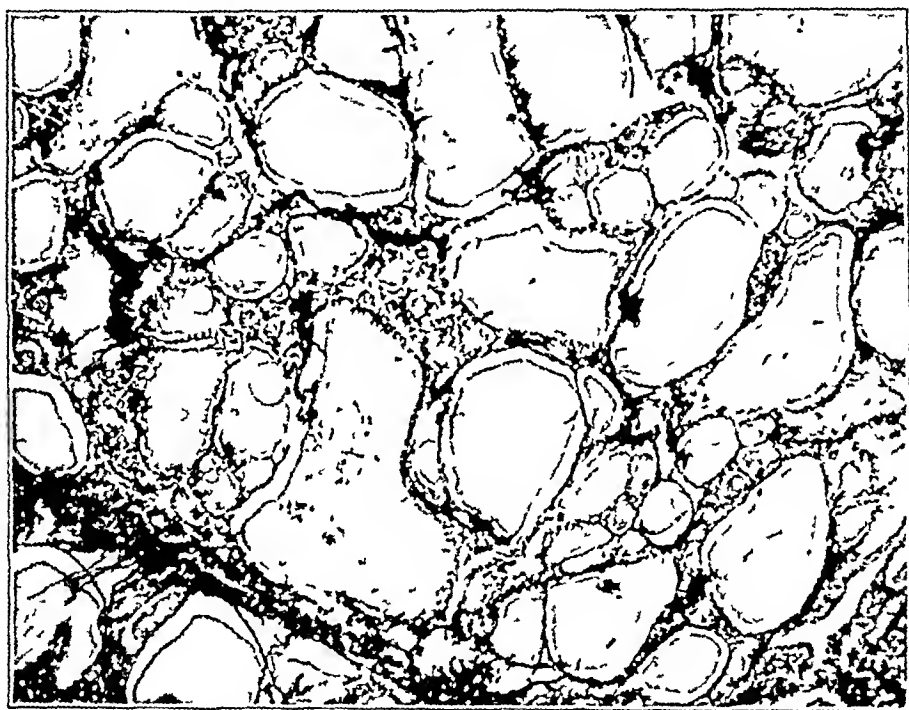


Fig 10 (case 34)—Struma nodosa colloidica macrofollicularis, clinically with hyperfunction Van Gieson, $\times 75$

The removed tissue weighed 45 Gm, and consisted of three pieces, 6 by 4 by 2, 4 by 2 by 1 and 3.5 by 1.5 by 1 cm

Microscopic examination of the specimen showed large follicles with flat epithelium and deeply staining colloid In other parts sections with small follicles, lined by tall columnar epithelium, partly desquamating, were seen Small infiltrations of lymphocytes were numerous in these parts

The histologic diagnosis was struma diffusa basedowiana (fig 3)

The tests showed

Iodine content, 0.560 per cent of dry substance

Effect on the tadpoles, very strong (no 9 in fig 11, fig 4)

Effect on the rat, + 161 mm of mercury

CASE 11—B N, an unmarried woman aged 45, always lived in California (bay region) She knew of her goiter only one month before the operation The symptoms were typical, but not severe and consisted of nervousness, palpitation,

tremor, loss of weight and increased appetite. No exophthalmos was present. Treatment with iodine was not reported.

The removed tissue weighed 27 Gm, 7.5 by 3 by 1.8 and 4.5 by 3 by 1 cm.

Microscopic examination showed the follicles to be predominantly small, with pale to medium staining colloid and lined by tall cuboidal epithelium, which was desquamated in many follicles. Infiltrations of lymphocytes were frequent.

The histologic diagnosis was struma diffusa parenchymatosa basedowiana.

The tests showed

Iodine content, 0.029 per cent of dry substance.

Effect on the tadpoles, slight (no. 11 in fig. 11).

Effect on the rat, not determined.

CASE 13—A. A., a housewife and teacher, aged 33, lived in different parts of Canada, and for the last three years in California (Lake Tahoe region). She was nervous during the last seven years. The cardinal symptoms developed after salpingectomy and appendectomy sixteen months before the operation for goiter and became more severe after ten months. The symptoms were typical, consisting of nervousness, tachycardia, palpitation, hyperhidrosis, increased appetite, diarrhea, muscular weakness and exophthalmos. Graefe, Stellwag, Moebius' signs were positive. Treatment with compound solution of iodine (0.6 cc three times a day) was administered two and one-half weeks before the operation.

The removed tissue weighed 30 Gm, and consisted of two pieces measuring 4.5 by 3 by 1.6 and 5.5 by 2.5 by 2 cm.

Microscopic examination of the specimen showed that the follicles were small to medium in size, with medium stained colloid which showed serrated edges in some instances. The epithelium was high columnar, in many follicles in two and three layers. Collections of lymphocytes were infrequent.

The histologic diagnosis was struma diffusa parenchymatosa basedowiana.

The tests showed

Iodine content, 0.228 per cent of dry substance.

Effect on tadpoles, medium (no. 13 in fig. 11).

Effect on the rat, not determined.

CASE 14—B. V., a housewife, aged 25, lived in California (central plain) all her life. Symptoms of goiter began one and one-half years before the operation. She was treated with compound solution of iodine on alternate weeks, some months before operation. She felt relieved at first, but four months before the operation, after she had discontinued taking iodine for a while, she became worse. She did not take any iodine until nine days before the operation (0.6 cc three times a day) at which time the basal metabolic rate was 61.4 per cent plus. The symptoms were typical, consisting of nervousness, tremor, hyperhidrosis, tachycardia, increased appetite, loss of weight (15 pounds [6.8 Kg.] during the last two months). Exophthalmos was marked. Graefe, Stellwag and Moebius' signs were positive.

The removed tissue weighed 27.5 Gm, and consisted of two pieces 5 by 3 by 2.5 and 5 by 3 by 2 cm.

Microscopic examination showed a "classic picture." There were rather uniformly small follicles with little or no colloid. The colloid was faintly stained and vacuolated. The epithelium was tall columnar, partly desquamated, forming papillae in many follicles. Small areas of lymphocytes were present. There was no sign of involution.

The histologic diagnosis was struma diffusa parenchymatosa basedowiana (fig 5)

The tests showed

Iodine content 0.196 per cent of dry substance

Effect on the tadpoles, slight (no 14 in fig 11 fig 6)

Effect on the rat not determined

CASE 29—T. A., a girl, aged 14, lived in northern California until the age of 9, and in the bay region ever since. She had had goiter and symptoms for two years. She was treated intermittently with iodine (amount not known) which relieved the symptoms temporarily but they became worse when the treatment was discontinued. During the last few months preceding the operation the illness became more severe. When the patient entered the hospital she showed the typical picture of exophthalmic goiter: nervousness, palpitation, tremor, tachycardia (from 100 to 120), loss of weight and increased appetite. Exophthalmos was present, and the Stellwag, Gräfe, Moebius' signs were positive. The basal metabolic rate was 80.8 per cent plus (Benedict-Talbot) or 81.5 per cent plus (Benedict-Hendry-Baker). The patient was treated with compound solution of iodine (0.6 cc three times a day) three weeks before the operation, under which treatment she improved.

The removed tissue weighed 106 Gm., and consisted of two pieces, measuring 7.5 by 5 by 3 and 8 by 4 by 4 cm.

Microscopic examination of the specimen showed many medium to large follicles, filled with pale to medium staining colloid and lined by flat to low cuboidal epithelium, proliferating in places. The colloid was vacuolated in many follicles. Areas with very small follicles and tall columnar epithelium, forming papillae, were present. Here the follicles were empty or filled with little pale colloid. Lymphoid tissue in the form of small follicles to large infiltrations was abundant. There was no increase of fibrous tissue.

The histologic diagnosis was struma diffusa basedowiana.

The tests showed

Iodine content, 0.318 per cent of dry substance

Effect on the tadpoles, very strong (no 29 in fig 11)

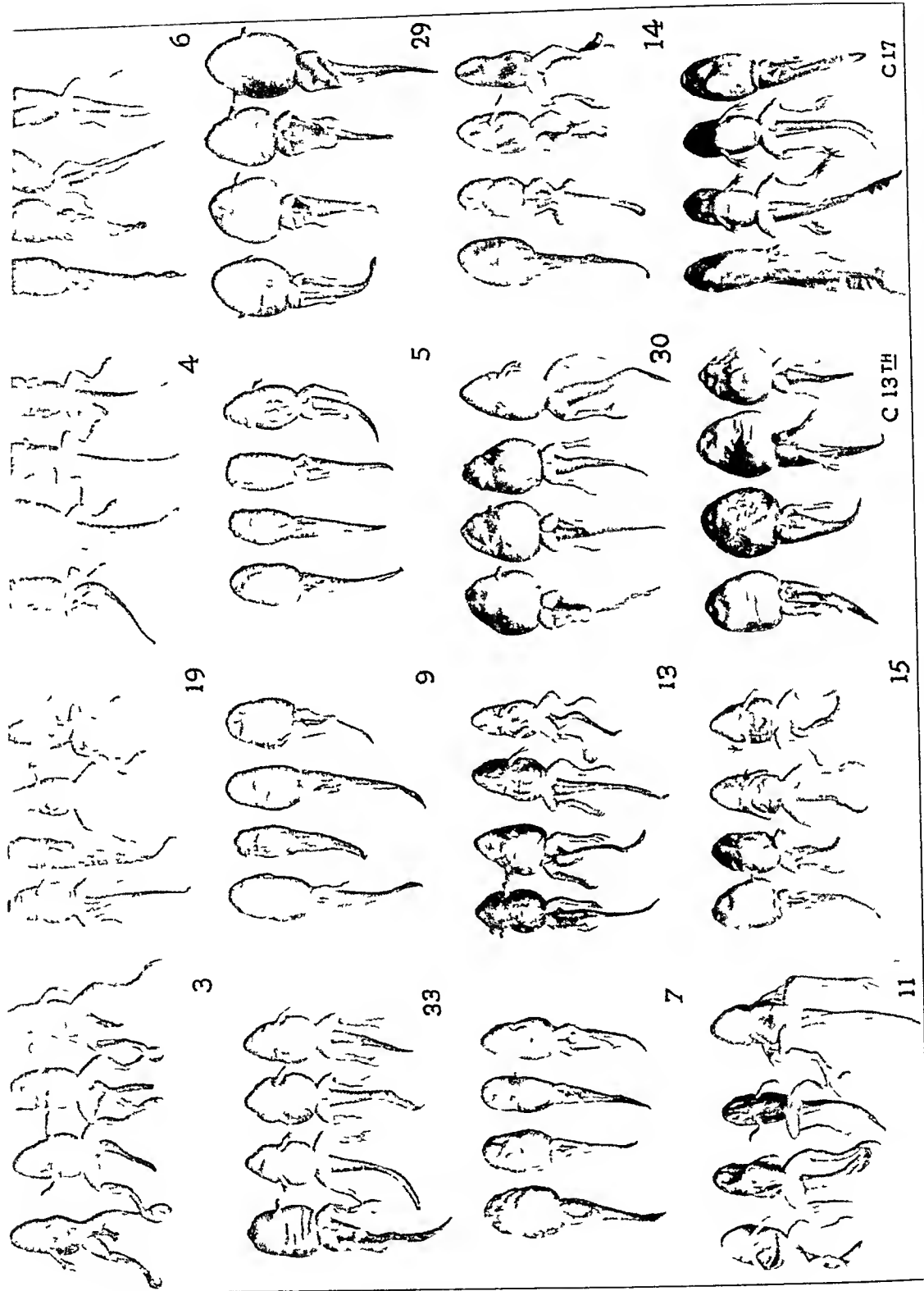
Effect on the rat + 115 mm. of mercury

CASE 30—H. E., a married woman, aged 42, lived in Montana and Idaho 0-25, then on the Pacific coast and for the last year in the bay region. She had symptoms of hyperthyroidism for one year, and a definite goiter for from three to four months. The symptoms were typical and severe, consisting of nervousness, palpitation, excessive perspiration, tachycardia (from 100 to 110), increased appetite and loss of weight (20 pounds [9 Kg.] in six months). No exophthalmos was present. The patient was treated with compound solution of iodine (0.6 cc three times a day) for one month before operation.

The removed tissue weighed 60 Gm., and consisted of two pieces measuring 6 by 4 by 2.5 and 5 by 3.5 by 2 cm.

Microscopic examination showed the great majority of the follicles to be medium to large in size, with scant colloid in general, and flat epithelium. In some follicles the epithelium proliferated and was cuboidal to columnar. Throughout the sections were areas with small follicles with no or little colloid, lined by tall columnar epithelium. Small collections of lymphocytes were present.

The histologic diagnosis was struma diffusa basedowiana.



Figs 11 and 12—Effect on the metamorphosis of the tadpoles. The animals are reproduced in about one fourth natural size. C4, C8 and C17 are normal controls, fed liver and lettuce. C5th and C13th are controls fed with thyroid tablets (Burroughs and Wellcome). The other figures are the numbers of the cases. The animals of case 1 and 2 and of eleven controls have not been reproduced.



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18



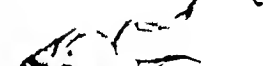
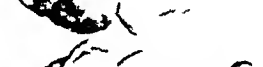
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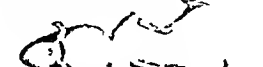
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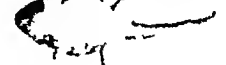
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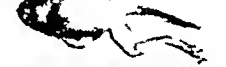
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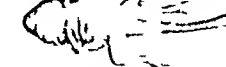
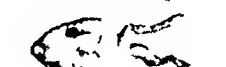
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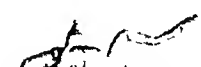
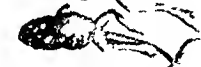
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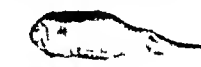
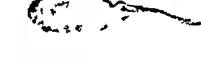
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25



C5TH



C4



C8

CORRELATION BETWEEN CLINICAL AND PATHOLOGIC GOITER TYPES AND BIOLOGIC ACTIVITY AND IODINE CONTENT OF GOITER SUBSTANCES

Case	Iodine Content, per Cent (Dry Substance)	Clinical Symptoms	Effect on Tadpoles (Average Time of Death in Days)			Effect on Rat, Affected Tadpole	Colloid Content (I-Substituted)	Histologic Diagnosis	Duration of Goiter, toms, Years	Age of Patient	Yes, amount and time used not known
			(1) Experimental Tadpole	(2) Control Tadpole	(3) Difference 1-2						
13	0.115	Hypofunction basal metabolic rate, 10% super imposed by hyper function?	22 1/4	19	1-1 1/4	++	++	Struma diffusa colloides et nodosa colloidesc nonproliferans	?		
6	0.0523	Indifferent	Killed after 90	13	(77)*		0 to ++	Struma nodosa macrofollicularis et proliferans et nodosa parenchymatosa microfollicularis	11	?	19
1	0.0714	Indifferent	Killed after 90	12	(77)		++ to +++	Struma nodosa macrofollicularis nonproliferans et nodosa parenchymatosa microfollicularis	12		13
19	0.0372	Indifferent	60	15	13	+50	++ to ++	Struma nodosa macrofollicularis proliferans et nonproliferans	25		49
5	0.0390	Indifferent	55 1/2	12	15 1/2	+60	0	Struma nodosa parenchymatosa partum trabecularis	More than 5		78
25	0.0411	Indifferent	60	15	45		++ to +++	Struma nodosa colloides macrofollicularis nonproliferans et nodosa parenchymatosa microfollicularis	23		55
24	0.0301	Indifferent	34 1/4	15	19 1/4	+89	++ to ++	Struma nodosa colloides macrofollicularis partum proliferans	5		68
35	0.103	Indifferent	23	19	+1		++ to ++	Normal gland with a few nodules (struma nodosa colloides microfollicularis nonproliferans)	?		12
Control	0.1		12, 13, 15, 19			+171					
31	0.0605	Mild or questionable, basal metabolic rate, +15%	54 1/4	15	+33 1/2		0 to ++	Struma nodosa parenchymatosa microfollicularis	18	6 mo	10
26	0.0672	Mild	55 1/2	15	+40 1/2		++ to ++	Struma nodosa colloides macrofollicular (partum basodivertita) et nodosa parenchymatosa microfollicularis	20	3	67
28	0.0675	Slight hyper function?	41	15	+26		++ to +++	Struma nodosa colloides macrofollicularis proliferans et nodosa parenchymatosa microfollicularis			
23	0.0980	Mild	42	15	+27		s+ to ++	Struma nodosa colloides macrofollicularis proliferans et parenchymatosa microfollicularis	2	6 mo	34
											Probable 2 years ago

The tests showed

Iodine content, 0.208 per cent of dry substance

Effect on the tadpoles, strong (no. 30 in fig. 11)

Effect on the rat, + 115 mm of mercury

THE IODINE CONTENT

The two extremes found in this group were 0.029 and 0.56 per cent. The average iodine content of the goiters of seven patients treated with compound solution of iodine was the highest of all the groups, 0.3194 per cent. The goiter of the only untreated patient showed an iodine content considerably below normal. Both results are in agreement with the findings of a number of other authors (Branovačky,²⁴ Holst and Lunde²⁵). Branovačky, for instance, gave as an average for untreated severe cases 0.0547 per cent and for mild cases, 0.0223 per cent.

A certain relationship exists between the iodine content and the quantity of iodine administered before operation, as the patient with the highest percentage was treated for three months and the one with the lowest for only nine days. But between these two extremes there exists no correlation whatsoever. The patients in cases 5 and 7 were both treated with the same amount, and the percentages were 0.246 and 0.480.

THE COLLOID CONTENT

Section V of the table shows clearly that the colloid content is parallel to the iodine content, confirming the well known fact that treatment with iodine increases the colloid content, described by A. Kochei, Cattell,²⁶ and later especially by Rienhoff.²⁷ Recently, however, some authors particularly Hellwig,²⁸ pointed out that the high colloid content too often is attributed to the preoperative treatment with iodine. He claimed that goiters of Graves' disease with rich colloid but with flat epithelium are not "lugolized hyperplasia" but diffuse colloid goiters with beginning "basedowification" and that these can always be distinguished from goiters in which the colloid content increased as a result of treatment with iodine by the taller epithelium.

²⁴ Branovačky (footnotes 4 and 9)

²⁵ Holst, J., and Lunde, G. Intermediate Iodine Metabolism During the Preoperative Treatment of Exophthalmic Goitre, *Am J Surg* **7** 39, 1929

²⁶ Cattell, R. The Pathology of Exophthalmic Goitre, Boston M. & S. J. **192** 989, 1925

²⁷ Rienhoff, W. F. Histologic Changes Brought About in Cases of Exophthalmic Goitre by Administration of Iodine, *Bull Johns Hopkins Hosp* **37** 285, 1925

²⁸ Hellwig, C. A. Form und Funktion des nordamerikanischen Kropfes, *Arch t. klin. Chir* **154** 1, 1929

in the large follicles. I agree that the diagnosis of 'lugolized hyperplasia' is made too often. As a rule, a consideration of the patient's history will decide.

The biologic activity showed a complete dependence on the iodine and colloid content in this group. However, it is to be said that slight deviations might have been found in a greater number of cases. The biologic activity, as already mentioned, was lower than in the adenomas with hyperfunction, although they were clinically more active and the iodine content was higher. The fact that adenomas are much less vascularized than the diffuse gland and that they are devoid of lymph vessels might suggest that their higher biologic activity is due to incomplete resorption of the active substances. None of the goiters was more active than the thyroid tablets of Burroughs and Wellcome.

Section V of the table also shows that in this group there is no relationship whatsoever between the clinical and the biologic activity. The two extremes, the goiter in cases 14 and 9, are of special interest. The goiter in case 14 was clinically very severe, with a basal metabolic rate of plus 61.4 per cent after three days of treatment with iodine, and the goiter showed the old classic picture of the *struma diffusa parenchymatosa basedowiana* with little or no colloid (fig. 5). The biologic activity was very slight, as figure 6 demonstrates. It was even lower than in case 24, a clinically indifferent *struma nodosa colloidosa*. The biologic activity of the goiter in case 11, in which the patient had not been treated with iodine, was even less active. Unfortunately the tests on rats could not be made in these cases.

On the other hand, the goiter in case 9, which showed a moderate clinical hyperfunction (basal metabolic rate + 52 per cent before the treatment with iodine) was very active in both tests (fig. 4). Wegelin and Abelin²⁹ and Brianovačky¹ each reported one case of goiter with the typical picture of the *struma diffusa parenchymatosa basedowiana* which failed to induce or showed only a very slight effect on the metamorphosis of the tadpoles. The goiter in the case of Wegelin and Abelin showed only traces of iodine, in the case of Brianovačky, it was richer in iodine. Preoperative treatment with iodine is not probable in either of these cases.

The study of Williamson, Peaise and Cunningham¹¹ revealed the same fact on a greater number of goiters. Nine specimens of *struma diffusa parenchymatosa* with little or no colloid, which had not been treated with iodine before the operation, failed to induce metamorphosis. Six of these goiters contained no iodine (determined with the method of von Fellenberg) and three very little (0.008, 0.009

29 Wegelin and Abelin (footnote 2, second reference)

and 0.064 per cent) Furthermore, 500 Gm of moist material of the same untreated type was digested after the method of Harrington, and the digest was precipitated with acid The precipitate, which contained 1.04 per cent iodine, was neutralized and fed to tadpoles without accelerating the metamorphosis Iodine-treated, colloid-containing goiters of Graves' disease were not tested

It would lead too far to discuss the theory these authors developed from their findings But they show, together with Wegelin and Abelin, Brianovačky and my findings, that untreated or insufficiently treated, but clinically very active, glands of Graves' disease can have little or no effect in the Gudeinatsch test On the other hand, there are cases reported in which the goiters had a very low iodine and colloid content and which were biologically very active For instance, the goiter in a case of Wegelin and Abelin (1921) with 0.011 per cent iodine content was at least as active as the thyroid tablets (Bulloughs and Wellcome) and therefore as active as the goiter in case 9 of my series with 0.560 per cent iodine, and with the highest biologic activity, about fifty times higher

How are these facts to be explained? Recent investigations on the iodine metabolism show the action of the iodine on patients with primary exophthalmic goiter Von Fellenberg,³⁰ and Veil and Sturm³¹ showed that in cases of primary thyrotoxicosis the iodine content of the blood is always increased Holst and Lunde²⁵ confirmed these findings, and furthermore, by separating the blood iodine by von Fellenberg's method into the alcohol-soluble inorganic and the alcohol-insoluble organic fraction, demonstrated that not only the percentage of the total but also the percentage of the organic blood iodine is greatly increased in patients with primary exophthalmic goiter According to these authors the figures for the inorganic fraction are considerably heightened during the administration of iodine, while the organic fraction "is reduced to the normal or almost to the normal figures and the fall is practically parallel to the decrease of the metabolism figures" At the same time, as is well known, a retention of the colloid and iodine in the goiter occurs These investigations therefore would suggest that the effect of the administration of iodine can be explained merely by the law of mass action thus confirming the view of different clinicians who called it diastically a "constipation" of the gland It is, however, hardly conceivable that there should not be enough thyroxin (and other active substances) left in a gland which is still so active as to maintain a high basal metabolism to induce metamorphosis

30 von Fellenberg, T. Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods, *Ergebn d. Physiol.* **25** 176, 1926

31 Veil, W. H., and Sturm, A. *Deutsches Arch. f. klin. Med.* **147** 166, 1925

Romeis³² showed that a solution of thyroxin 1:100 000 000 is still definitely active. Therefore, the theory of Plummer, and of other authors, that in advanced stages of primary exophthalmic goiter the gland produces an abnormal, incompletely iodized thyroxin, would gain support assuming, however, that this abnormal thyroxin, probably together with other substances would only act on the metabolism but not on the metamorphosis. Swingle³⁴ showed that acetyl-thyroxin induces metamorphosis in tadpoles but does not act on the metabolism. The same authors' point of view, that the gland is exhausted sooner in one patient and later in another, would explain the fact that goiters with little iodine and colloid are active in the Gudernatsch test in the one case and inactive in the other.

It is difficult to decide, from the work of the earlier workers and from the experiments reported here whether the struma diffusa parenchymatosa basedowiana is brought back to normal in its biochemistry and in its function by treatment with iodine, a view held by Marine³ and other authors. It is a well established fact that the struma basedowiana is more active (with certain exceptions mentioned before) than the clinically indolent diffuse colloid goiter, both in the Gudernatsch and in the Asher-Streuli test. But unfortunately only a few normal glands have been subjected to these tests. Wegelin and Abelin³⁵ have two normal glands in their series which were both as active as the thyroid tablets of Burroughs and Wellcome but the same was true of the only untreated struma basedowiana. Branovačková⁴ found that two normal glands were on the average slightly less active than the strumae basedowianae which probably had not been treated with iodine. In the series reported here three iodine-treated strumae diffusae basedowianae were decidedly more active than the specimen in case 35 which consisted mainly of normal thyroid tissue. Three others were only little less active. This would therefore suggest that under the treatment with iodine in certain cases the potency of the gland is actually not decreased but increased. Only investigations on a larger scale, including biologic tests, will be able to solve this problem.

COMMENT

The reported findings show that the correlation between the iodine and colloid content, and between the iodine content and the biologic

32 Romeis, B. Biologische Versuche ueber die Wirksamkeit verschiedener Thyreoideapraeparate. *Ztschr f d ges exper Med* **4** 379, 1916, **5** 99, 1917, **6** 101, 1918.

33 Plummer, H. S., and Boothby, W. M. The Value of Iodine in Exophthalmic Goitre, *J Iowa State M Soc* **14** 66, 1924, footnote 21.

34 Swingle. *Am J Physiol* **70** 208 1921.

35 Wegelin and Abelin (footnote 2, first reference).

activity, of adenomas in California is not so great as in the material in Cleveland (Marine¹³) but is greater than in the material in Bern (C. Abelin³) and in Munich (Spatz,¹⁰) The extremes in a given group generally follow the rule that those with the higher iodine content are richer in colloid and are biologically more active than those with low iodine content The deviating results might be due, as Spatz¹⁰ suggested, to the more widespread use of iodine in areas of endemic goiter

The relationship between the iodine content and the clinical activity of adenomas seems to be much closer, in agreement with the reports of Wegelin and Abelin,² Branovačky²⁴ and Spatz¹⁰ The iodine content increases from the low figures of the clinically indifferent cases through the clinically slight to the clinically severe hyperactive adenomas

The comparison of the iodine content and the biologic activity of adenomas in California, an area on the periphery of an endemic, with those found in centers of endemics is of special interest The iodine content of clinically indifferent adenomas of different histologic structure ranged within the same limits, as the one in Freiburg (Germany), Munich (Germany), Bern (Switzerland) and Cleveland (Ohio) However, low figures as in Bern and Cleveland were not found The group of clinically hyperactive adenomas showed a considerably higher iodine content than all the adenomas in the localities mentioned before

The biologic activity of clinically indifferent adenomas was about the same as in Bern and in Munich, to judge from the comparison with the effect of standardized thyroid substances On the other hand, the biologic activities of the adenomas with hyperfunction was higher than the one of all the types of goiters in Bern This fact might be attributed to the higher iodine content It is impossible to compare the results with those in the other regions of endemic goiter, since no standard effect was determined there

The relationship between the iodine content and the biologic activity as compared with the action of thyroid tablets of Burroughs and Wellcome, is of great interest Three clinically very active adenomas with an iodine content of 0.163 to 0.276 per cent were biologically more active than the thyroid tablets with 0.4 per cent (fig. 7), whereas two strumae diffusae basedowianae with a higher iodine content (0.560 and 0.480 per cent) were slightly less active, and one of this series with 0.560 per cent was approximately as active as one of Wegelin and Abelin's³⁵ with 0.011 per cent

It is evident that in the iodine-treated goiters of primary Graves' disease not all the iodine is present in an active form One must assume the same for the normal thyroid substance, if one does not

accept the point of view that in the adenomas with hyperfunction the iodine occurs in a more active form. All these considerations lead to the conclusion that not the quantity but the quality of the iodine compounds determine the biologic and clinical activity of normal and goitrous glands ³⁶

Different facts clearly indicate that the adenomas with hyperfunction differ biologically from the diffuse goiters of primary Basedow's disease. The relation between the iodine content and the clinical activity is rather constant in adenomas, but is entirely missing in the iodine-treated struma basedowiana, in which the biologic activity is parallel to the iodine content. The biologic activity of the latter is high when under the successful treatment with iodine the symptoms of hyperthyroidism have partly subsided. No instance of a clinically hyperactive but biologically inactive adenoma has even been reported, as in the case of struma diffusa basedowiana ³⁷. All these differences greatly support the view of Plummer ²¹ and others that a fundamental difference exists between the two forms of hyperthyroidism.

A dysfunction of the various types of goiter seems at the present time the most discussed problem. It was advocated for the struma basedowiana by Moebius and is today supported especially by Plummer ²¹ and by de Quervain ¹⁸. The results of the experiments reported here together with those of other authors seem to substantiate their view. Wegelin and Abelin ⁹ demonstrated a dysfunction of different types of goiters in their experiments on tadpoles. The same was found in two adenomas of this series. Furthermore, the deviation of the results of the two biologic tests suggests the existence of a secretion changed in its quality, but not in the same manner as in the adenomas and in the goiters of Graves' disease. No results as to the nature of these different forms of dysfunction have been brought forward in this investigation.

³⁶ Harington and Randall (The Chemical Assay of Thyroid Gland, *Quart J Pharm & Pharmacol* **2** 501, 1929) showed that the thyroxin-iodine varies between 28 and 60 per cent of the total iodine.

³⁷ It is impossible, from these experiments, to decide whether this is due to morphologic factors (lower degree of resorption) or to the biologic properties of the products of secretion.

GRANULOPENIA (GRANULOCYTOPENIA)

WITH SPECIAL REFERENCE TO CLASSIFICATION AND BENIGN TYPES^{*}

GEORGE M. PIERSOL, M.D.

AND

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PHILADELPHIA

The syndrome first described by Schultz¹ as agranulocytosis was considered by him to represent a definite clinical entity. Other observers who also held this view based their opinions on the fairly uniform clinical history, particularly the age and sex predilection and the peculiarity in the distribution of the supposedly specific lesions. However, subsequent contributions have indicated that a similar hematologic picture occurs with varying clinical features and apparently is based on a variety of causes. Later observations have strengthened the view that the disease is symptomatic of a number of etiologic factors, such as infection, chemical agents and the action of x-rays and radium. The protagonists of the theory that the disease is a distinct entity believe (1) that it represents a specific primary disease or infection of the granulopoietic structure in the bone marrow with the necrotic lesions in the mouth as an expression (Schultz), or (2) that the lesions in the mouth form the primary focus of a specific infection. The opponents of this conception agree that there is an abnormal response to the various types of infection or chemical poisons with diminution or disappearance of the granulocytes, they believe that this defect is probably due to differences in distribution or to actual injury of the granulopoietic mechanism with destruction or lack of production in these cells. An attitude of compromise is taken by Dahlen and Wahlgren,² who believe that the condition is the result of infection acting on a predisposition in the form of hypoplasia of the myeloid structures. These conflicting views not only have created a controversial aspect in the discussion of granulopenia but have indicated the necessity for a more precise terminology and a more careful subdivision of these various

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^{*} From the Graduate School of Medicine, University of Pennsylvania, and the Laboratories of the Jewish Hospital.

1 Schultz, W. *Deutsche med. Wchnschr.* **48** 1495, 1922.

2 Dahlen, B., and Wahlgren, F. *Acta med. Scandinav.* **65** 407, 1926.

groups. Not the least important is the removal of the equivocal designation of agranulocytosis. Among the earliest authors to prefer the term granulocytopenia was David.³ Based on analogy with such terms as "leukopenia" and "thrombopenia," we see no objection to the abbreviated term of granulopenia which has been adopted recently by Roberts and Kracke.⁴

We believe that the syndrome described by Schultz merits the term of primary granulopenia and that instances without discoverable cause and corresponding to his original description should properly fit into this category. This premise would rest on a sounder basis if it were possible to lay down certain criteria in the same manner in which one now distinguishes pernicious anemia from secondary anemia. The term secondary granulopenia seems appropriate for the larger group of cases due to known causes. A satisfactory classification not dissimilar to the one recently advocated by Roberts and Kracke is as follows:

Primary Granulopenia

- (a) Acute (Schultz)
- (b) Chronic (recurrent)

Secondary Granulopenia

- (1) General infections
 - Influenza
 - Typhoid
 - Some exanthemas
 - Sepsis, etc
- (b) Focal infection
- (c) Chemical (arsphenamine, benzene)
- (d) Irradiation (x-rays, radium)
- (e) Blood diseases (leukemia, splenic diseases, aplastic anemia, etc)

PRIMARY GRANULOPENIA

The characteristic clinical features of primary granulopenia or agranulocytosis of Schultz, Friedemann,⁵ and others have been described so frequently that it suffices here to review briefly the salient features. In a typical case, an acute febrile illness occurs in a middle-aged woman with prostration, usually mild jaundice, sore throat and necrotic ulcerative or gangrenous lesions in the mouth, pharynx and vagina. Lesions in other parts of the digestive tract, such as in the esophagus, stomach, colon, rectum and anus have also been described. The leukocyte count is profoundly depressed affecting mainly the granulocytes, with a corresponding predominance of lymphocytes. The polymorphonuclear cells may fall to lower than 10 per cent or may be entirely absent on smears. At the same time, there is little or no change in the red cells, hemoglobin or platelets. The spleen and liver are slightly enlarged. Death usually occurs within one month, in milder cases there may be recovery.

3 David, W. *Med Klin* **20** 1614, 1924

4 Roberts, S. R., and Kracke, R. R. *Ann Int Med* **5** 40 (July) 1931

5 Friedemann, N. *Med Klin* **19** 1357, 1923

At necropsy the bone marrow shows erythropoietic function, but the granulocytes are few. However, younger forms, such as myeloblasts and eosinophilic myelocytes, may be found. Myelocytes showing evidence of degeneration are also noted.

SECONDARY GRANULOPENIA

In contrast with the rather rare primary types are the relatively more common instances of depressed granulocyte counts associated with

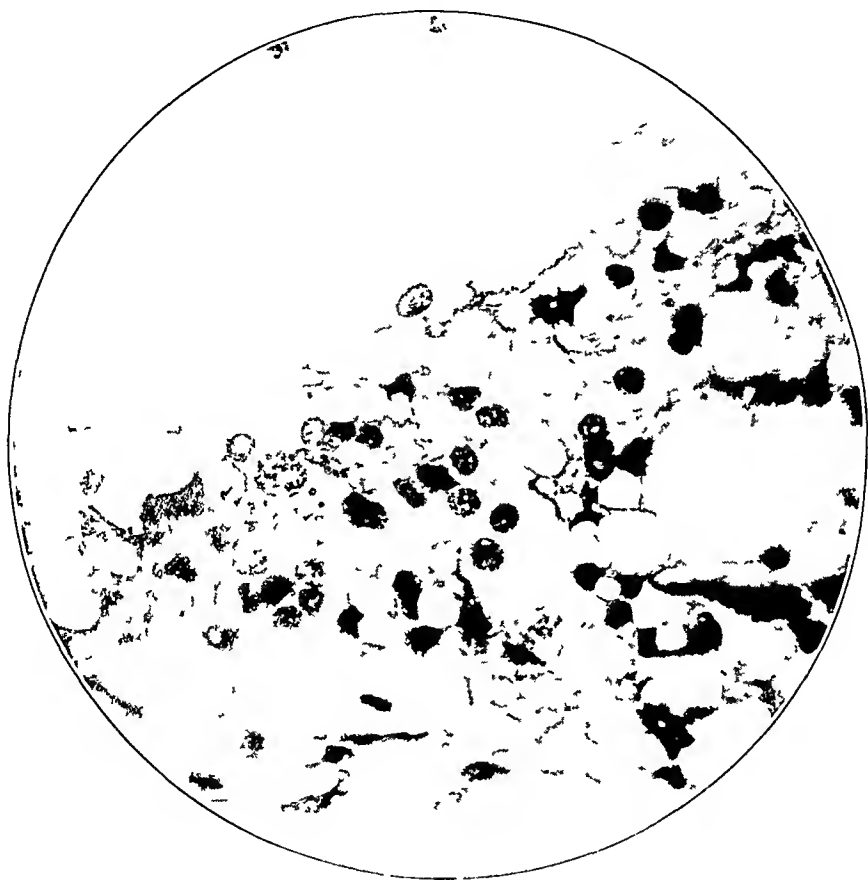


Fig 1—Smear from sternal marrow (postmortem) in a case of diffuse bone marrow injury following the administration of neoarsphenamine. In the center are seen a number of macroblasts (erythroblasts) with typical "cart wheel" nuclei, toward the periphery are several megaloblasts with fine vesicular nuclei. Lack of maturation of both myeloid and erythroid series is noted. No myelocytes or polymorphonuclear cells were found in any field.

general or focal infections, with conditions caused by arsphenamine, benzene and other chemical agents, or by the x-rays and radium or with a less general aplastic state of the bone marrow, as in certain anemias. It seems more appropriate to designate such conditions as secondary types or to consider them all as does Duke⁶ as belonging

⁶ Duke W W. Aplastic Anemia, *J A M A* 91:720 (Sept 8) 1928.

to the general class of aplastic anemia and varying in degree or in the selective character of the aplasia. Among these types, that induced by arsphenamine has been well studied in recent years. Usually this type is associated with other signs of diffuse aplasia, such as a lowered number of red cells and platelets. Occasionally, the anemia is further increased by marked hemorrhage due to thrombopenia. It seems more likely to occur when the arsphenamine is given to a syphilitic patient who shows evidence of anemia. A typical instance observed by us was

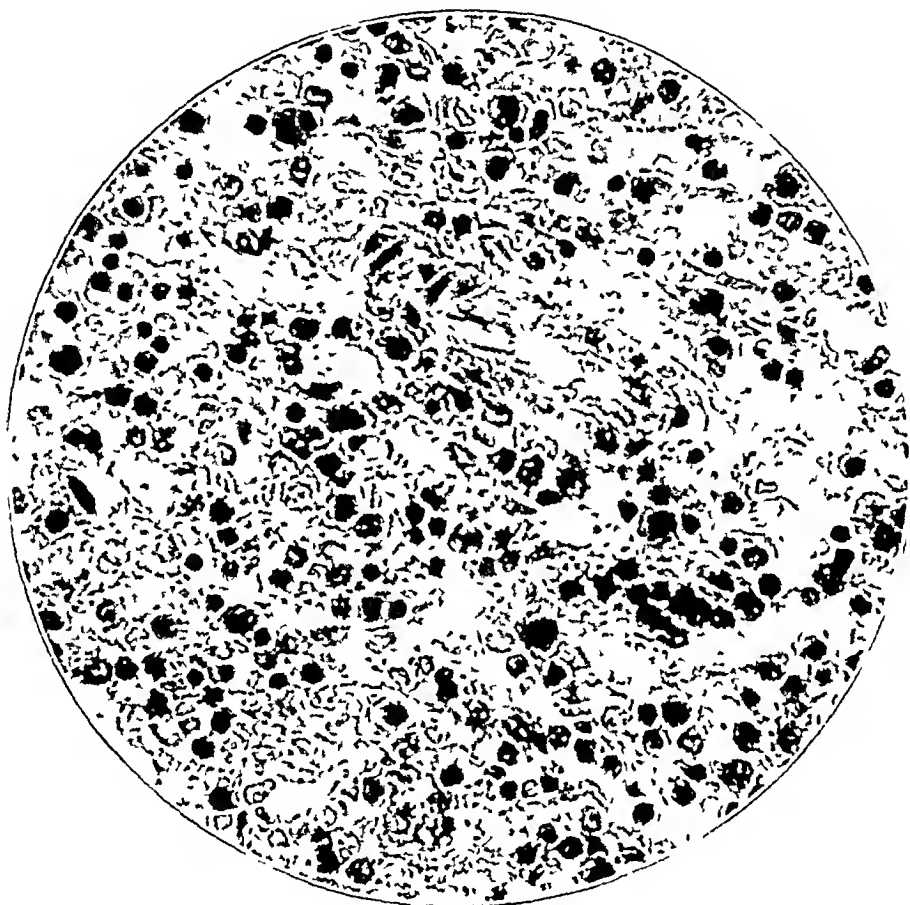


Fig 2—Section from marrow of femur in a patient presenting secondary granulopenia from sepsis. Normoblasts, macroblasts and megaloblasts are present, but myeloid series are represented by a few myeloblasts and degenerated myelocytes.

recently described.⁷ The patient, an Italian woman, aged 45, had severe anemia and a positive Wassermann reaction. Though she was treated cautiously with small doses of neoarsphenamine, granulopenia developed, and there was a further lowering of the red cells and hemoglobin. The last leukocyte count on the day of death was 850, and neutrophils were absent in the blood smears. A series of similar instances was recently reviewed by Farley.⁸ He does not believe that the arsenic in

7 Steinfield, E, and Shay, H. *M Clin North America* **13** 923 (Jan) 1930.

8 Farley, D. *Am J M Sc* **179** 214, 1930.

the arsphenamine molecule is the cause of the phenomenon. There are several possible explanations, there may be (1) an idiosyncrasy to the arsphenamine per se possibly creating a benzene-like action on the bone marrow or (2) a form of Herxheimer reaction with the liberation of myelotoxic substances. The latter theory appears plausible in view of the fact that in the past patients who were not syphilitic and who suffered from severe secondary anemia or pernicious anemia have at times shown improvement from the empiric use of arsphenamine.

The granulopenia secondary to irradiation is well known and has frequently been described. Granulopenia is symptomatic of various diseases of the blood and lymphatic structures. In the leukemias it appears to be due to interference with the formation of mature cells due to intense proliferation or infiltration of the leukemic cells in the bone marrow. We have occasionally seen depressed bone marrow function in carcinoma, lymphosarcoma and other malignant conditions in the absence of demonstrable invasion of the bone marrow. Whether this is due to some obscure toxic factor or to the inability of the bone marrow to cope with the demands resulting from cachexia and a disordered nutritional state we are unable to say.

The occurrence of a granulopenic blood picture in septic states has been described in a recent article by Blumer,⁹ who emphasizes the difficulty in distinguishing such cases from aplastic anemia and leukopenic stages of leukemia.

Our interest in the occurrence of moderate granulopenia associated with focal infection and ending in recovery was aroused by the following case:

CASE 1—History—B. H., a school girl, aged 7, was admitted to the Graduate Hospital, Nov. 1, 1929, with a painful swelling of the right side of the lower jaw. There was no history of familial or hereditary diseases. With the exception of measles, the previous medical history was uneventful.

Two weeks before admission, the patient had a slight sore throat. Six days before admission, the right lower molar was extracted. Following this, the jaw became swollen, and a temperature of 103 F. developed. The patient was treated in the clinic and improved, but again became worse and was admitted to the hospital.

Examination—Physical examination on admission revealed an undernourished girl who appeared toxic, the temperature was 102 F. No icterus of the sclerae was noted. The area of the right mandible was swollen and tender. Small round white ulcers were present on the lips. The inner surface of the lower lip was covered with white plaques of oval contour with central depressions varying in size from that of a pinhead to that of a pea. A halo of reddened mucosa surrounded these areas. The right lower first molar and the second premolar were absent, and a swelling was present along the ramus of the mandible. The tonsils were reddened and cryptic but not much enlarged, no exudate was present on them. The sub-

⁹ Blumer G. *Am J M Sc* **179** 11, 1930.

maxillary group of cervical lymph nodes was enlarged a soft mitral systolic murmur was present, the pulmonic second sound was accentuated. The lungs were clear. The spleen was palpable. No genital lesions were present. On admission the leukocyte count was 2000 with the neutrophils 20 per cent or a total of 400 cells per cubic millimeter.

Course—After forty-eight hours the temperature began to fall the leukocyte count had risen to 4800 and the labial ulcerations began to heal. On November 5, there was marked general improvement, and the leukocytes had risen to 10,200, with the total number of granulocytes 27 per cent. The recovery in the number of granulocytes was preceded by a slight increase in the metamycocyte group. The red cell and hemoglobin counts were lowest on admission, the red cells being 3,610,000 and the hemoglobin, 64 per cent the maximum count was noted eleven days after admission, namely 4,560,000 red cells and 71 per cent hemoglobin. Blood platelets varied from 194,000 to 230,000, the volume index was 0.78. Reticulocytes varied from 0.3 to 0.4 per cent. Cultures of the blood were sterile. The treatment, which was almost entirely local, was administered under the direction of Dr. Ivy. Though stimulating doses of roentgen irradiation for the long bones and injections of foreign protein were considered, improvement began before these measures were actually inaugurated.

The second case illustrates granulopenia associated with focal infection occurring as part of a general aplastic blood picture.

CASE 2—History—B. C. B., a white woman, aged 40 single, was admitted to the Graduate Hospital on June 23, 1928 with the complaint of pain and swelling of the legs. The family history was not relevant. The past history was uneventful until 1918, when the patient had a nervous collapse necessitating complete rest. The present illness began in April, 1928, when the patient noticed that it was difficult to walk rapidly. It became increasingly difficult to raise the legs, and later cramplike pains were noted in the calf of the right leg. The ankles then became swollen and discolored. Pallor and general weakness appeared.

Examination—Examination revealed a pale undernourished, asthenic woman. No icterus was noted. Ecchymoses were present above both knees on the anterior aspect of the thigh and in both popliteal spaces.

Hyperreflexion was present there was no absence of vibratory sensation. Examination of the upper part of the respiratory tract made by Dr. R. H. Skillern showed hyperplastic ethmoiditis on the left side. The tonsils were buried, cryptic and badly infected, with free pus. Tonsillectomy was advised.

Dental caries were noted in the second right upper molar and gingivitis along the gingival line of the upper right molars. A roentgenogram showed a slight infection around the second upper right molar and a broken root fragment in the region of the upper right bicuspid.

The heart was normal, with the exception of a moderate, bell-like aortic second sound. No enlargement of the liver or spleen was found there were no palpable masses. Orthopedic examination made by Dr. W. G. Elmer showed that the right knee was pathologically flexed (20 degrees). The hamstrings were tense and contracted. Pelvic examination (made by rectum) gave normal results.

Laboratory examinations showed blood sugar, 129 mg and blood urea nitrogen, 10 mg per hundred cubic centimeters. The Wassermann and Kahn reactions of the blood were negative. Fractional gastric tests showed free hydrochloric acid present in all specimens, ranging from 5 to 35. No ova or parasites were found in stools.

Urinanalysis showed a positive reaction to acid, a specific gravity of 1.017, no albumin, no sugar and no casts

Course—With extra nourishment and the ingestion of liver and hematinics, the blood count gradually improved. When the leukocyte count, which was 1,700 on admission, reached the satisfactory level of 7,600, tonsillectomy was done (Jul 31). After this, the patient gradually improved in strength and in ability to walk, though she was inhibited greatly by a listless and apprehensive attitude.

Blood platelets varied from 125,000 to 209,000. The coagulation time was seven minutes, the clot retraction, normal, and the bleeding time, two minutes.

Blood Counts in Case 2 on Various Days

Date	Hemo globin	Red Cells	White Cells	Neutro phils	Eosino phils	Baso phils	Lympho cytes	Mono cytes
6/28/28	36	2,000,000	1,700—	46		3	49	2
7/ 6/28	55	3,290,000	2,000	56			43	1
7/10/28	60	3,560,000	5,750	52		1	44	3
7/ 7/28	64	3,640,000	2,150	57			37	6
7/26/28	59	3,438,000	7,600	57	1		38	4
8/ 6/28	72	3,650,000	5,300	50			48	2
8/20/28	72	4,150,000	5,200	68			29	3

In addition to the well defined primary granulopenia of Schultz and the cases that are clearly secondary, instances are encountered that fail to fit definitely into either group, as for example that of the patient with recurring cycles of granulopenia described by Rutledge, Hansen-Pruss and Thayer¹⁰. Somewhat similar cases have been reported recently by Roberts and Kracke.⁴

Thompson¹¹ described a syndrome characterized by a febrile illness associated with leukopenia, lymphadenopathy, palpable spleen and the late appearance of white spots on the posterior part of the pharynx. The author had unusual opportunities to study some of these patients prior to the appearance of the disease. All of the seven patients who were described in this report recovered, despite the fact that in two cases cell counts showed the absence of polymorphonuclear cells. Though the condition in some of the cases also resembled infectious mononucleosis the usual age predilection was absent.

In a series of ten patients presenting the agranulocytic syndrome described by Rosenthal,¹² there was one, a woman, aged 52, who showed a normal relative proportion between the polymorphonuclear cells and the lymphocytes, though the total leukocyte count was only 900. The author designated this case as "aleukocytic angina."

A critical survey of these somewhat atypical and borderline cases raises the question as to whether or not they may be regarded as variants

¹⁰ Rutledge, B. H., Hansen-Pruss, O. C., and Thayer, W. S. *Bull. Johns Hopkins Hosp.* **46**: 369 (June) 1930.

¹¹ Thompson, W. P. *Am. J. M. Sc.* **180**: 232, 1930.

¹² Rosenthal, N. *New York State J. Med.* **30**: 695, 1930.

in the scale between the typical primary granulopenias and the secondary varieties

There are undoubtedly many persons otherwise normal, who exhibit a definite tendency toward granulopenia. This fact has been strikingly demonstrated by Roberts and Kiacke,⁴ who found from careful analysis of the blood counts of 8,000 patients that about 25 per cent show granulopenia, and that this group of persons exhibit fatigue, weakness, exhaustion and somnolence more readily and to a greater degree than those with normal granulocyte counts. In this class of granulopenic persons, they found that 56 per cent were women, the majority of whom were between 40 and 60 years of age.

These observations are significant when considered in the light of the age period when primary granulopenia is most common. Furthermore, it is not unreasonable to suppose that this group is particularly susceptible to the obscure factor that is responsible for acute granulopenia.

EXPERIMENTAL STUDIES

With the thought of studying the mechanism of granulopenia rather than with any hope of throwing light on its etiology, we have endeavored to imitate the blood picture in this condition. For this purpose we have used inoculations of a small group of common bacteria. Rabbits were the only animals used. The following strains were selected: anhemolytic, hemolytic and green streptococci, *Bacillus influenzae* (Pfeiffer), pneumococcus (type I), *B. coli*, *B. typhosus*, *B. proteus* and *Staphylococcus aureus*. The inocula consisted of (1) the bacteria in suspension, (2) Berkefeld filtrates of broth cultures, (3) supernatant fluids of cultures inactivated by cresol, U. S. P., after three days' incubation, (4) agar plus bacteria and homologous blood plus bacteria to produce infected foci in the hyperergy experiments. The first three were injected subcutaneously, intramuscularly and intravenously. The infected foci were produced in the loose tissues of the flank. In addition to the effects of simple injections, the effects of an altered state of reactivity of the experimental animal were studied with the thought that these factors may create widely different responses in individuals to the same group of organisms. This is of particular application in instances of granulopenia that are definitely associated with septic or local infections due to organisms that usually produce leukocytic response. We are mindful of the fact that emphasis has been placed on these altered states by various observers in recent years. Swift, Derick and Hitchcock¹³ have studied the production of hyperergy induced by infected agar foci in an attempt to reconcile conflicting ideas of the importance of certain strains of streptococci in the production of rheumatic fever. Though it cannot be said that there exists any similarity between the attempt to produce a proliferative and exudative rheumatic lesion and the disease under discussion, there is a point of comparison between these experimentally infected foci and the focal infections occasionally associated with granulopenia. We have also studied the phenomenon¹⁴

13 Swift, H. F., Derick, C. L., and Hitchcock, C. H. Bacterial Allergy to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, *J. A. M. A.* **90** 906 (March 24) 1928.

14 Arneith, J. *Die qualitative Blutlehre*, Leipzig, J. A. Barth, 1920.

recently described by Schwartzman. This involves the reaction in a previously prepared site induced by the injections of bacterial filtrates into the skin of a rabbit followed by an intravenous injection of the same filtrate twenty-four hours later. The intradermal amounts are small, from 0.25 to 0.5 cc, but the intravenous doses are large, from 0.5 to 3 cc per kilogram. In the prepared area of skin the reaction is characterized by violent hemorrhagic and necrotic reactions coming on from four to five hours after the second injection. The short incubation period distinguishes this from the well known Arthus phenomenon. Though these lesions contain polymorphonuclear leukocytes, the study of the blood during the various phases of this reaction was undertaken because of a remote resemblance to clinical cases in which necrotic lesions have suddenly appeared in the mouth within a short time after dental extractions.

In all these experiments, the blood counts were made on blood from the ear veins of the rabbits. Though the counts taken in this manner are apt to vary considerably, the results of such determinations are satisfactory if they are made under uniform conditions and with suitable precautions. Since the results of these studies will be reported in detail later, it suffices to give a brief summary of the main points.

EXPERIMENTAL RESULTS

1 The subcutaneous injections of suspensions of all the organisms used produced a leukocytosis varying in degree with the animal and with certain strains. No long-continued fall in leukocytes was induced by any of the filtrates or by the production of a state of hyperergy. With the exception of the leukopenia following intravenous injections, described later, the Schwartzman phenomenon produced no continued leukopenia.

2 Intravenous injections of inactivated cultures in broth, supernatant fluids of broth cultures, Berkefeld filtrates of typhoid cultures and, to a lesser extent, the broth mediums alone produce the following phenomenon: a sharp fall of the leukocytes to approximately one fourth of the original amount within from fifteen to fifty minutes, this affected the polymorphonuclears almost entirely, at times monocytes disappeared during the lowest counts.

At the time of the recovery of the leukocyte count which usually began from two to four hours after the injection, stained smears showed large proportions of young forms of neutrophils and pseudo-eosinophils. In supravital preparations stained with neutral red, the return of the granulocytes was ushered in by an influx of motile forms. The bone marrow of a healthy rabbit apparently withstands this demand on granulopoiesis fairly well, in view of the observation that the same fall and recovery could be induced three or four times with several days of rest between the periods. The bone marrow of the femur was examined at the end of these observations and contained approximately the usual erythroid-myeloid ratio.

The effect of intravenous injections of peptone and like substances has been noted for a number of years. Arneth¹⁴ fully discussed this

phenomenon in 1920 Koskowsky and Zahrzewski¹⁵ have more recently described the changes in all the cells of the leukocyte series during peptone shock Beard and Beard¹⁶ have shown that the sharp fall in neutrophils initiated by peptone will also occur with intravenous injections of 1 per cent and 2.5 per cent solutions of sodium chloride. However, the leukocyte count returned to normal more rapidly than had been previously noted in experiments with peptone.

COMMENT

In the light of recent studies made by Sabin¹⁷ and others on the physiology of bone marrow, we believe that a clearer understanding of disturbed granulocytic function is possible. From these studies it appears that granulopoiesis differs from erythropoiesis in the manner of distribution of these cells in relation to the endothelium lining the intersinusoidal capillaries of the bone marrow. Whereas the most immature of the red cells lie against the endothelium within the lumen of the vessels, the most mature of the granulocyte series (myelocyte, C metamyelocyte and leukocyte) lie outside the lumen, but against the capillary wall, the metamyelocyte and the leukocyte enter the lumen in normal circumstances. The mechanism of cell delivery involves both a vasomotor and a chemical factor. In addition, there must be present the mechanism of maturation. Therefore, leukocytosis involves both an increased delivery of cells and, if the necessity continues, the increased maturation of myelocytes, first of the older forms, and then of the younger. Sabin has considered two hypothetical factors, a chemotactic factor, *C*, and a maturation factor, *M*. The same author has also demonstrated an approximately hourly rhythm in the number of white cells, with rises in the afternoon independent of ingestion of food. Neutrophils die out in showers, as indicated by corresponding increases of non-motile cells in supravital preparations. They are promptly replaced, either directly from the bone marrow or from a reservoir such as the spleen. It is probable that on stained smears, the nonmotile cells correspond to (1) cells the cell membranes of which are ruptured, with well stained granules near by, (2) free nuclei with some poorly stained granules in close proximity to the cell, (3) pale cells out of which all the granules seem to have dissolved, leaving a pale structureless cytoplasm. We have occasionally seen large numbers of this third group of cells in severe septic infections, particularly those associated with bacteremia. Motile polymorphonuclear cells in supravital preparations

¹⁵ Koskowsky, W., and Zahrzewski, A. *Compt. rend. Soc. de biol.* **96**, 56, 1927.

¹⁶ Beard, L. A., and Beard, J. W. *Am. J. Phys.* **85**, 169, 1928.

¹⁷ Sabin, F. R. *Bull. Johns Hopkins Hosp.* **37**, 14, 1925, *Physical Rev.* **8**, 191, 1928.

stained with neutral red show active motion with streaming of granules and staining of granules and vacuoles. The nucleus should not stain if the dye is in correct proportion.

So far as one may apply observations made on laboratory animals and on patients suffering from benign forms of granulopenia to the more severe fatal forms, it seems possible that the mechanism is similar in all. Varying degrees of severity may depend on the duration or the potency of the harmful agent and the constitutional make-up of the individual. Sudden removal of older leukocytes is followed by attempts to replace these by younger forms in a more or less orderly fashion in mild cases. In severe cases there is apparently an abeyance of granulopoiesis, or there may be disorderly distribution with a throwing-out of still more immature forms. In the latter instances, it would appear that the hypothetic chemotactic factor is active while the maturation factor is absent. Clinically we have seen both of these reactions following asphenamine therapy, in one, there was produced a granulopenic picture, in the other, a blood picture indistinguishable from myeloblastic leukemia.

In regard to our own experiments, we can only state that a long-continued granulopenia could not be induced in healthy rabbits by the use of a small group of common bacteria in the form of suspension, filtrates or inactivated supernatant fluids. The assumption of a probable altered state of reactivity (from an immunologic point of view) as a factor in these disturbances was not borne out by these results. This, of course, does not dispose of the obscure conditions conveyed by the terms idiosyncrasy or constitutional susceptibility. The positive results in the production of short periods of granulopenia with intravenous injections of peptone and other substances followed by the characteristic influx of young forms on recovery are of interest mainly in their resemblance to milder forms of granulopenia. Although these phenomena are based on well known observations, their application to the granulopenias merits renewed interest and further investigation.

HODGKIN'S DISEASE WITH CAVITY FORMATION IN THE LUNG

REPORT OF A CASE *

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AND

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Almost a century ago, Hodgkin described the disease that bears his name. It has many varying clinical and roentgenologic aspects, and has been the subject of numerous publications. The disease invades various organs and systems of the body, and is often difficult to diagnose. Longcope¹ enumerated the possible confusions, and especially stresses our liability to fail in differentiating tuberculosis from Hodgkin's disease. If further investigations substantiate the belief of L'Esperance² that the avian tubercle bacillus is responsible for Hodgkin's disease, the similarity and so-called coexistence of the two diseases in one subject will be explained. In discussing a series of 173 cases, in 85 of which there were lesions of the chest, Burnam³ stated that only 8 presented pleural effusions, but "pictures simulating tuberculosis were commoner." This same difficulty of differentiating the two diseases appears constantly in reports of cases by Longcope,¹ Burnam,⁴ Whitaker,⁵ Lemon and Doyle,⁶ Walton,⁷ and others.

Our case is unusual in that roentgenograms taken periodically throughout the period of treating the patient showed the formation

* Submitted for publication, June 17, 1931

1 Longcope, W T, in Osler and McCrae. Modern Medicine, ed 3, Philadelphia, Lea & Febiger, 1927, vol 5, p 226

2 L'Esperance, Elise S. Studies in Hodgkin's Disease. Cancer, International Contributions to the Study of Cancer in Honor of James Ewing, edited by Frank Adair, Philadelphia, J B Lippincott Company, 1931

3 Burnam, C F. Hodgkin's Disease, with Especial Reference to Its Treatment by Irradiation, J A M A **87** 1445 (Oct 30) 1926

4 Burnam, C F. Lymphosarcoma and Hodgkin's Disease, W Virginia M J **25** 395 (July) 1929, footnote 3

5 Whitaker, L R. Malignant Lymphoma (Hodgkin's Disease). A Radiographic Study, Arch Int Med **32** 538 (Oct) 1923

6 Lemon, W S, and Doyle, J B. Clinical Observations of Hodgkin's Disease with Special Reference to Mediastinal Involvement, Am J M Sc **162** 516 (Oct) 1921

7 Walton, H J. Roentgenological Examination of the Mediastinum, Am J Roentgenol **5** 181 (April) 1918

and continuance of a cavity in the lung. In view of the difficulty, previously mentioned of differentiating tuberculosis from Hodgkin's disease, this cavity might readily have been thought to be one of a tuberculous nature.

Beside biopsy, which is conclusive in diagnostic value, there is what Whitaker⁵ termed the "roentgen-ray therapeutic test", that is the rapid reduction of the glands under roentgenotherapy. MacRae⁸ is even more emphatic than Whitaker. He said, "the hyperplastic glands of Hodgkin's disease respond in an almost spectacular manner to radiation treatment. In fact, shrinking under the influence of x-rays is almost pathognomonic."

Cases in which tuberculosis has been known to be a complicating disease are recorded by Schreiner and Mattick,⁹ and Weber.¹⁰ T. B. and T. K. Menon¹¹ reported a case in which the two, tuberculosis and Hodgkin's disease, existed at the same time. Our case might have been similar to these, and as suggested before, might have been considered tuberculosis, except that when the case came to necropsy, tissue taken from the lining of the cavity proved to be lymphogranulomatous.

A careful review of the literature has failed to reveal another case analogous to ours, though Weber,¹⁰ in February, 1930, reported a case which was diagnosed both clinically and anatomically as bronchial carcinoma, and in which he recorded the roentgenologic finding in the chest of what is "probably a cavity." The existence of this cavity was not substantiated at necropsy. It was only after the microscopic examination of necropsy material that the diagnosis of lymphogranuloma was made, whereas our patient was referred to us for roentgenotherapy for Hodgkin's disease, all the findings were substantiated by necropsy. The first roentgenogram showed that the case belonged to type 1 of the Wessler and Greene¹² classification. It also conformed to the shadow of Hodgkin's disease as described by Childs.¹³

8 MacPae, J. D. Hodgkin's Disease, *Radiol. Rev. & Chicago M. Rec.* **51** 525 (Dec.) 1929.

9 Schreiner, B. F., and Mattick, W. L. Results of Radiation Therapy in Leukemia and Lymphogranuloma, *J. Cancer Research* **8** 504 (Dec.) 1924.

10 Weber, Herbert. Lungenlymphogranulome, *Beitr. z. path. Anat. u. z. allg. Path.* **84** 1 (Feb. 14) 1930.

11 Menon, T. B., and Menon, T. K. Coexistence of Lymphadenoma and Tuberculosis, *Brit. M. J.* **1** 1037 (June 8) 1929.

12 Wessler, Harry, and Greene, C. M. Intrathoracic Hodgkin's Disease. Its Roentgen Diagnosis, *J. A. M. A.* **74** 445 (Feb. 14) 1920.

13 Childs, S. B. New Growths Within the Chest. X-Ray Diagnosis, *Am. J. Roentgenol.* **10** 175 (March) 1923.

REPORT OF CASE

History—G M, a farmer, aged 28, white, was referred to us by Dr Casper F Hegner on March 15, 1924, for roentgenograms of the chest and roentgen treatment for Hodgkin's disease. The patient was married, and had one child 4 years old. He was one of six children, all living, his father and mother were living, and all the family were well except his mother who was undergoing treatment at our office for carcinoma of the lip.

The patient had measles, whooping cough, tonsillitis, influenza (1918) and grip often though not severely, and the latest attack occurred four years previously. He smoked a pipe steadily.



Fig 1—Roentgenogram of the chest made March, 1924, showing a large mass in the upper mediastinum. Note the increase in soft tissues of the neck.

Eighteen months before consulting a physician, he noticed a lump in the left anterior cervical glands just above the clavicle, and the whole left side of the neck swelled. Fourteen months later, there was a similar involvement of the glands on the right side. The patient said that the glands were larger when he had a cold and that he caught cold easily, and coughed severely. His normal weight was between 145 and 155 pounds (65.8 and 70.3 Kg). His appetite was poor, and he had no digestive disturbance other than constipation. He slept poorly on account of difficulty in breathing.

Physical Examination—The patient was well nourished, weighed 141 pounds (64 Kg), and was 5 feet 8 inches (172.7 cm) in height. His pulse was 112, and the blood pressure 130 systolic and 80 diastolic. His tongue was coated, he had a slight shortness of breath, and some hoarseness. His neck was greatly enlarged.

on both sides (Figure 1 shows the increase in soft tissues about the neck) There were large, diffuse, nonpainful, discrete nodules of different consistency filling the neck on both sides from the clavicles to the upper plane of the thyroid The larynx was nonadherent There were enlarged glands in both axillae, and small glands in each groin

Examination of the chest showed dullness fused with the base of the heart anteriorly, and paravertebral dullness to the seventh dorsal spine posteriorly

Roentgen examination showed a large, irregular, lobulated mass in the upper mediastinum All evidences of individual lymph nodes were obliterated (fig 1)

Course—Roentgenotherapy resulted in reduction of cervical, axillary and inguinal glands, and relief from symptoms Roentgenograms taken in February, 1925, eleven months after beginning treatment, showed great reduction of the mass in the upper mediastinum (fig 2)



Fig 2—Roentgenogram taken eleven months later, February, 1925, showing great reduction of the mass in the upper mediastinum

In January, 1926, the process seemed to be quiescent, in March, the patient had acute coryza with a slight cough which became severe The following month the mediastinal shadow was even narrower than in January, but there was a large, well defined, homogeneous shadow at the hilus of the right lung, and a small, similar one at the hilus of the left lung (fig 3) At this time, the roentgenograms began to resemble those described by Wessler and Greene¹² as type 4, "discrete nodes at the roots of the lungs" In October, 1926, there was considerable reduction of the area at the hilus of the right lung, and slight clearing of the one on the left, which had been small before (fig 4) This reduction followed periodic roentgenotherapy

Eleven months later, the patient began to lose weight, and reported that he had a cough for the previous month, but no other symptoms At that time, the roentgenograms showed great increase in the involvement at the hilus of the right lung, infiltration into the right upper lobe, and a moderate sized area in the paren-



Fig 3—Roentgenogram taken fourteen months later, April, 1926, showing a narrow mediastinal shadow but a large, well defined, homogeneous shadow at the hilus of the right lung and a small one at the hilus of the left lung



Fig 4—Roentgenogram taken six months later, October, 1926, showing the area at the hilus of the right lung to be considerably reduced and the one at the hilus of the left lung to be slightly cleared



Fig 5—Roentgenogram taken eleven months later, September, 1927, showing greatly increased involvement at the hilus of the right lung, infiltration into the right upper lobe, a moderate sized area in the parenchyma of the middle lobe, a small area in the parenchyma of the left upper lobe and increased involvement about the hilus of the left lung

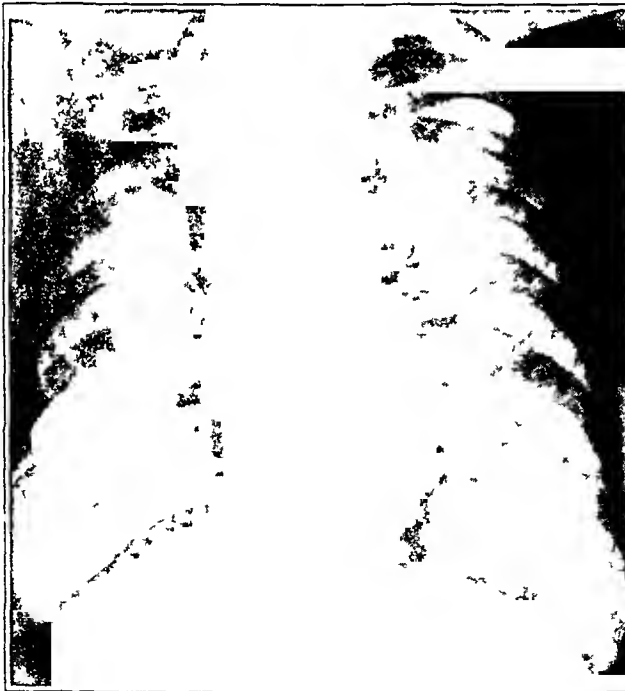


Fig 6—Roentgenogram taken four months later, January, 1928, showing clearing in the area in the middle lobe, a decrease about the hili, but extension of the area in the apex of the right lung



Fig 7—Roentgenogram taken one month later, February, 1928, showing an apparently beginning cavity formation in the apex of the right lung and a larger area in the parenchyma opposite the hilus of the right lung



Fig 8—Roentgenogram taken one month later, March, 1928, showing a well defined cavity in the apex of the right lung, an increase in the parenchymatous area opposite the hilus of the right lung and adhesions to the diaphragm on the right

chyma of the middle lobe. The left lung showed a small area in the parenchyma of the upper lobe, and some increase in the involvement about the hilus (fig 5).

A second course of treatment was begun at this time, three and one half years after the first series. In January, 1928, four months after instituting treatment, there was clearing of the area in the middle lobe, some decrease in the involvements about the hilus, but an extension of the area in the apex of the right lung. Otherwise, the patient's condition was about the same (fig 6).



Fig 9—Photograph of the right lung after necropsy, showing (A) cavity in the apex and (X) area taken for microscopic section from the wall of the cavity.

One month later, the left lung was unchanged, but the right lung showed what was apparently beginning cavity formation in the apex and a large area of involvement in the parenchyma opposite the hilus (fig 7).

The patient was uncomfortable and dissatisfied. His cough continued, and in March 1928, he was referred to one of the large clinics for diagnosis. The report from that group was "This is a case of chronic fibroid tuberculosis, especially of the right upper lobe, with cavity formation. Only slight adenopathy in the neck and none elsewhere at the present time." Treatment in a sanatorium was advised and it was thought that the case probably had been, but no longer was, Hodgkin's disease. We still maintained that the condition was Hodgkin's disease and not tuberculosis.

However, conforming with the suggestion made at the clinic, the patient was admitted to Agnes Memorial Sanatorium, Denver, on March 23, 1928. At that time, he was short of breath on slight exertion, fatigued easily, had night sweats,

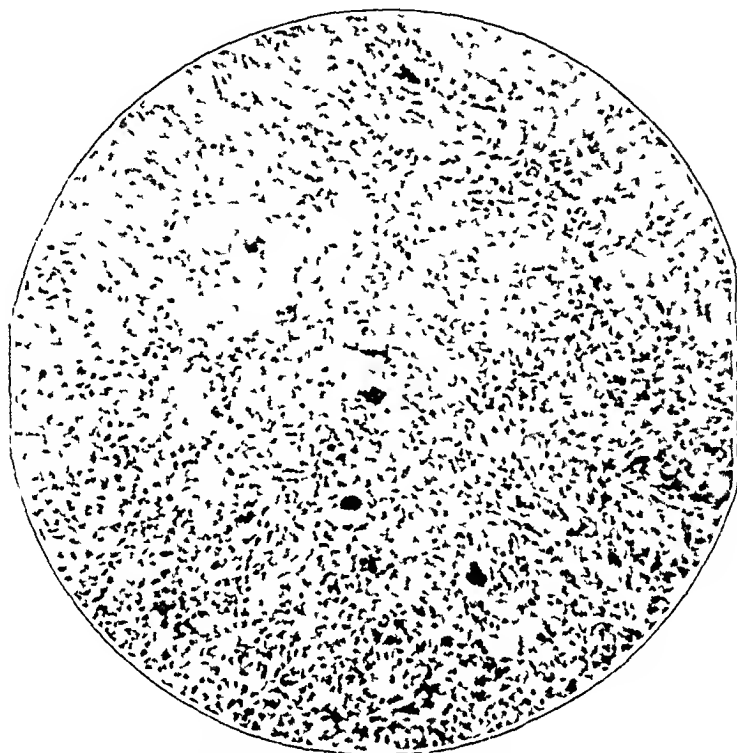


Fig 10—Photomicrograph of section taken from the wall of the cavity showing areas of hyaline degeneration surrounded by round or spindle cells in the stroma of the fibrous connective tissue

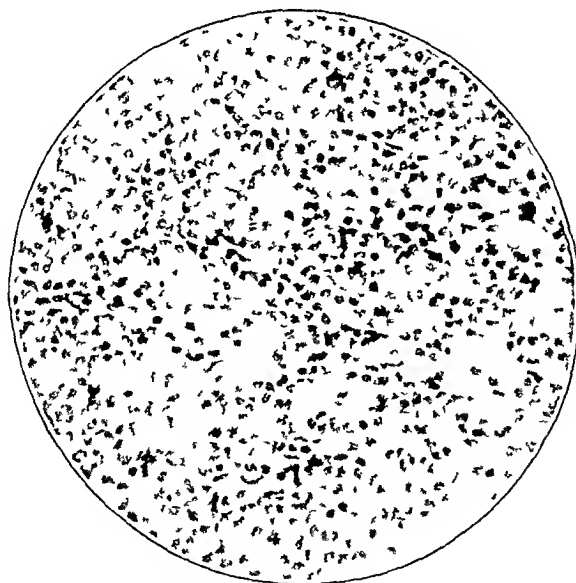


Fig 11—Same as figure 10, $\times 200$

slept poorly (averaged five to six hours) and did not feel rested in the morning. He had pain in the chest at times. He raised one-half cup of purulent sputum daily which was negative for tubercle bacilli on March 12. His weight was 132

pounds (59.9 Kg), his pulse rate 80 and respiratory rate 20, and his general condition was poor. The breath was foul, the tongue was coated, the mucous membranes and lips were pale, the skin and palms were dry and the fingers were clubbed and cyanotic. There was no cervical, axillary or inguinal adenopathy. The thyroid was nonpalpable.

Examination of the chest showed diminished resonance over the entire right lung, front and back, with increased tactile fremitus, harsh bronchial breathing was heard over the entire upper lobe, and increased dullness over the middle lobe, extending toward the apex, medium to coarse, moist râles were heard down to the fourth rib anteriorly, before and after coughing, none were brought out posteriorly on coughing. There was an amphoric area at the apex indicative of a cavity. On the left, there was diminished resonance over the entire lung with increased tactile fremitus, a few fine to medium râles were heard down to the third rib anteriorly after coughing, none were heard posteriorly.

In the roentgenograms at this time, the cavity in the apex of the right lung was positively defined, there was an increase in the size of the area in the parenchyma opposite the hilus of the right lung, and there were adhesions to the diaphragm on the right. The left lung was practically the same as in February (fig. 8).

No tubercle bacilli were observed in the sputum, though there were questionable acid-fast, clubbed rods in one specimen. Two guinea-pigs inoculated subcutaneously showed no pathologic lesion after three months. Except for a few hyaline casts, the urine was normal.

The medical director of the sanatorium did not concur in the diagnosis of tuberculosis made prior to admission. The patient died of pulmonary hemorrhage on June 3, 1928. Necropsy was performed by Dr. Philip Hillkowitz, the next day.

Postmortem Examination—The left lung was crepitant throughout, and there was a nodule in the upper lobe measuring 2 cm. in diameter. The right lung was adherent at the apex. There was a nodule in the upper lobe measuring 5 cm. and also a cavity 2 cm. below the apex which measured approximately 6 cm. in diameter. It was free from exudate, the lining was nodular and covered by a smooth membrane. There was a firm, grayish nodule 5 cm. in diameter in the middle lobe. The tracheobronchial lymph nodes were enlarged, firm, and of grayish color (fig. 9). There were no enlarged mesenteric nodes. The spleen showed slight enlargement, but there were no noteworthy changes in the liver or kidneys.

Sections taken through one of the nodules and from the wall of the cavity, when studied microscopically, revealed areas of hyaline degeneration surrounded by round or spindle cells in a stroma of fibrous connective tissue (fig. 10). There were many large, round, deeply stained cells showing several nuclei. These were apparently identical with the Sternberg or Dorothy Reed cells (fig. 11).

The anatomic diagnosis was lymphogranulomatosis of the lung with cavity formation.

COMMENT

The case presented is one of lymphogranuloma of the mediastinal type which in its later stages closely resembled tuberculosis. It was exceptional in that it developed a true cavity in the lung which also proved to be lymphogranulomatous when the case came to necropsy. We have been unable to find a similar case reported in the literature.

HEMANGIECTATIC HYPERTROPHY AND CONGENITAL PHLEBARTERIECTASIS

WITH PARTICULAR REFERENCE TO THE DIAGNOSTIC IMPORTANCE
OF THE PERIPHERAL VASCULAR PHENOMENA *

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The purpose of this communication is to present observations that should be helpful in the diagnosis of hemangiectatic hypertrophy. The term "hemangiectatic hypertrophy of a limb" denotes a condition of hypertrophy associated with increased vascularity of the affected extremity. This congenital or developmental increased vascularity may be due to dilatation of both the arteries and the veins, the term "congenital or developmental phlebarteriectasis" then being applied. Certain cirsoid aneurysms and plexiform hemangiomas of the scalp and face are probably of this nature. When the dilatation of the vessels is confined almost entirely to the veins, the term phlebectasis is applied. It should be noted that in phlebarteriectasis abnormal direct artery to vein anastomoses are not necessarily present, and that this condition is therefore to be differentiated from the more common traumatic or congenital arteriovenous aneurysms.

Fourteen cases of hemangiectatic hypertrophy recorded up to 1918 were summarized by F. Parkes Weber.¹ The reports of cases available for study will not be reviewed here, but references to these reports are given.²

* Submitted for publication, July 19, 1931.

¹ From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

² This investigation was aided in part by a grant from the De Lamar Mobile Research Fund of Harvard University.

1 Weber, F. P. Haemangiectatic Hypertrophy of Limbs—Congenital Phleb-arteriectasis and So-Called Congenital Varicose Veins, *Brit. J. Child Dis.* **15** 13 1918.

2 Weber (footnote 1) Harris, K. E., and Wright, G. P. A Case of Haemangiectatic Hypertrophy of a Limb and Observations upon Rate of Growth in the Presence of Increased Blood Supply, *Heart* **15** 141, 1930. Lewis, D. Congenital Arteriovenous Fistula, *Lancet* **2** 621, 680, 1930. Pemberton, J. J., and Saint, J. H. Congenital Arteriovenous Communications, *Surg., Gynec. & Obst.* **46** 470, 1928.

REPORT OF CASE

History—N B, a schoolgirl, 15 years of age, was admitted to the hospital for study on Feb 16, 1931. When she was 2 years old, the left hand was observed to be noticeably warmer than the right, and the veins of the left hand were unduly prominent. There was no history of trauma. As the patient grew older, the left hand and arm became larger and longer than the right. Six years before admission an operation was performed at another hospital in an attempt to correct the condition. The antecubital fossa was incised, but no abnormal artery to vein communications were found. The patient has felt entirely well. She states that the left hand and the lower part of the left arm feel warmer than the right and tend to perspire more readily.

Examination—Physical examination showed a bright, intelligent girl with no abnormalities save those related to the left arm and the vascular system. The heart was normal in size and position. The heart sounds were of good quality, and a soft systolic murmur was heard everywhere over the precordial area, particularly at the apex. Retrosternal dullness was normal in extent. In the left supraclavicular region coarse systolic and diastolic thrills were palpable, and systolic and diastolic murmurs could be heard. These signs were not transmitted into the left carotid artery but were easily elicited over the vessels of the left arm and forearm. A systolic thrill could be felt on grasping the left upper extremity firmly at any level between the apex of the axilla and the tips of the fingers. No evidence of abnormalities of intracranial blood vessels was present. Ophthalmoscopic examination of the fundi showed normal findings.

Capillary pulsation was visible in the fingers of both hands and over the forehead after it was stroked. These pulsations did not disappear after the left subclavian artery was compressed to the point of occlusion.

The patient was right-handed, but the left arm was obviously larger and longer than the right. At the medial border of the left antecubital fossa, there was an old, irregular scar measuring 7 cm by 2 cm in the greatest diameters. Beginning a short distance above the left elbow and increasing gradually in intensity down the arm, dusky cyanosis was evident (fig 1). The finger-nails and finger-tips of all the fingers of the left hand showed a more reddish cyanosis. The fingers of the left hand were longer and more slender than those of the right hand. Several small, red, irregular, cutaneous angiomas, varying from 0.5 to 2.5 cm in diameter were present over the left forearm and lower third of the left arm, particularly on the extensor surface. The color of these angiomas varied considerably in intensity on different occasions. The left brachial, radial and ulnar arteries were dilated and forcibly pulsating. Pulsation of the anterior interosseous artery was easily felt in the lower part of the left forearm. The veins of the left forearm and particularly those of the hand were abnormally dilated and prominent. The engorgement of what virtually amounted to a venous plexus over the fingers, hand and lower part of the forearm became conspicuous when the hand was placed in a dependent position. With the left arm 65 cm below the level of the right auricle, definite systolic pulsations were visible in the veins over the back of the left hand.

Heat, cold, touch, pain and pressure perception were normal. There was no astereognosis.

The red and white blood cell counts were within the limits of normal. Repeated urinalyses revealed no abnormalities. The Wassermann, Kahn and Hinton reactions of the blood of the patient and of the patient's mother were negative.

Special Studies—Electrocardiographic tracings were normal. Roentgenograms of the chest showed no abnormalities. The cardiac measurements from teleroentgenograms were as follows: from midsternum to right border of heart, 3.4 cm,

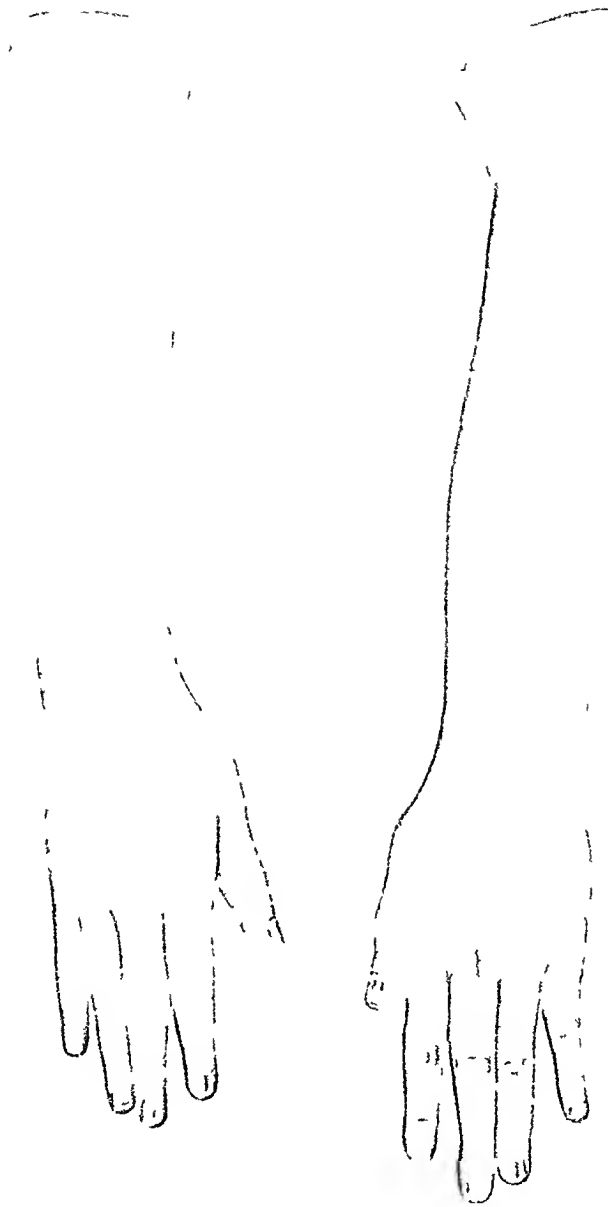


Fig 1—Hemangiectatic hypertrophy and congenital phlebateriectasis of the left arm, showing the hypertrophy, cyanosis and cutaneous angiomas of the left forearm and hand and the prominent veins over the hand and lower part of the forearm



Fig 2—Roentgenogram of the forearms, showing the increased length of the left radius and ulna

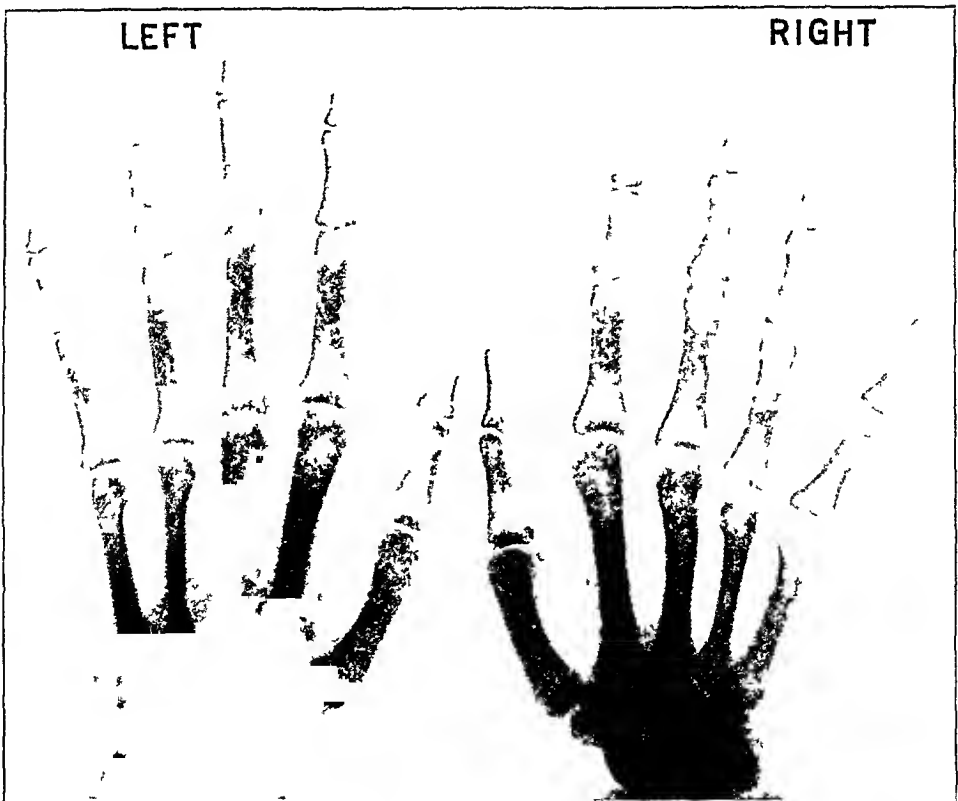


Fig 3—Roentgenogram of the hands, showing the increased length of the metacarpal bones and phalanges of the left hand

TABLE 1—*Linear Measurements of Bones of Upper Extremities*

Bone	Right, Cm	Left, Cm	Difference, per Cent
Humerus	33.2	34.0	2
Ulna	25.4	28.4	12
Radius	23.9	26.8	12
Metacarpals			
Thumb	4.6	5.0	9
Index	6.6	7.1	8
Middle	6.1	6.6	8
Ring	5.4	5.9	9
Little	5.3	5.7	8
Proximal phalanges			
Thumb	3.0	3.0	0
Index	4.6	5.0	8
Middle	4.3	5.0	16
Ring	4.1	4.8	17
Little	3.2	3.7	16
Middle phalanges			
Index	2.5	2.7	8
Middle	2.9	3.4	16
Ring	2.7	3.1	15
Little	1.9	2.2	16
Terminal phalanges			
Thumb	2.3	2.2	—4
Index	1.8	1.8	0
Middle	1.8	1.9	6
Ring	2.9	2.1	5
Little	1.7	1.7	0

TABLE 2—*Surface Measurements of Upper Extremities*

	Right, Cm	Left, Cm	Difference, per Cent
Lengths			
Tip of acromion process to styloid process of radius	32.2	37.0	9
Tip of acromion process to external condyle of humerus	29.8	30.5	2
Olecranon process of ulna to styloid process of ulna	25.4	28.3	11
Styloid process of radius to tip of middle finger	18.8	19.5	4
Base of proximal phalanx to tip of finger			
Thumb	6.1	6.2	2
Index	9.7	10.5	8
Middle	10.5	11.6	11
Ring	10.1	11.1	10
Little	8.0	8.5	6
Circumferences			
Arm at upper border of axilla	27.5	28.4	3
Arm, middle	22.9	24.6	7
Arm above condyles of humerus	21.0	23.2	10
Forearm, below elbow	22.0	23.8	8
Forearm, midportion	19.4	20.0	3
Forearm, above head of ulna	15.2	15.2	0
Hand at metacarpal phalangeal joint	18.4	18.8	2
Fingers			
Thumb, terminal phalanx, midportion	5.5	5.2	—5
Index, middle phalanx, midportion	5.1	4.9	—4
Middle, middle phalanx, midportion	5.1	4.6	—10
Ring, middle phalanx, midportion	4.8	4.4	—8
Little, middle phalanx, midportion	3.9	3.8	—3

TABLE 3—*Surface Areas of Upper Extremities*

	Right, Sq Cm	Left, Sq Cm	Difference, per Cent
Arm and forearm	1,032	1,174	14
Hand	384	407	6
Total upper extremity	1,416	1,581	12

from midsternum to left border of heart, 7.4 cm, total transverse diameter, 10.8 cm, transverse diameter of great vessels, 4.5 cm, transverse diameter of chest, 23.9 cm. Similar measurements from a teleroentgenogram taken during digital occlusion of the left subclavian artery showed no change.

Fluoroscopic observation of the heart shadow showed no perceptible changes in the cardiac excursion before and during digital occlusion of the left subclavian artery.

TABLE 4—Measurements of Cubic Volumes of Both Upper Extremities

Part of Extremity Measured	Right, Cc	Left, Cc	Increase	
			Cc	Per Cent
Arm	1,565	1,620	55	3
Forearm	750	935	185	24
Hand	285	315	60	21

TABLE 5—Measurements of Skin Temperature^{*}

Site of Measurement	Right, Degrees Centigrade	Left, Degrees Centigrade	Difference, Degrees Centigrade
Angle of jaw	31.2	31.1	0.0
Infraclavicular fossa	31.4	31.1	0.0
Arm			
Over head of humerus	31.4	31.8	0.4
Midportion, extensor surface	31.1	31.7	0.6
Midportion, flexor surface	31.7	32.5	0.8
Forearm			
Midportion, extensor surface	31.3	31.7	0.4
Midportion, flexor surface	32.1	33.0	0.9
Wrist			
Extensor surface	31.3	33.1	1.8
Flexor surface	32.3	33.2	0.9
Hand			
Dorsal surface	32.0	33.7	1.7
Palmar surface	32.3	33.4	1.1
Thumb			
Proximal phalanx, dorsal surface	32.2	32.3	0.1
Proximal phalanx, palmar surface	32.3	32.1	-0.2
Second phalanx of fingers, dorsal surface			
Index	32.3	33.1	0.8
Middle	32.4	33.5	1.1
Ring	32.2	33.6	1.4
Little	32.3	33.3	1.0
Second phalanx of fingers, palmar surface			
Index	31.4	33.4	2.0
Middle	31.8	33.9	2.1
Ring	31.6	33.5	1.9
Little	31.2	33.7	2.5
Tips of fingers			
Thumb	32.6	32.0	-0.6
Index	32.7	32.4	-0.3
Middle	32.7	33.0	0.3
Ring	32.6	33.3	0.7
Little	32.6	32.7	0.1

* The measurements given are those actually recorded at room temperature of 23 C and are not corrected to the standard temperature of 20 C.

Roentgenographic films of both upper extremities showed that the bones of the right arm were normal, while those of the left arm and hand were definitely longer (figs 2 and 3). Measurements of the bones of both upper extremities are recorded in table 1. Surface measurements of both arms are given in table 2. The surface area of the right upper extremity, calculated according to the formula of Du Bois,³ was 1,416 sq cm, of the left upper extremity, 1,581 sq cm. The surface areas of the arms and hands are presented in table 3. The cubic volume of each arm, measured by water displacement, is given in table 4.

3 Du Bois, E. F. Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1924.

The temperature of the skin of the left upper extremity, particularly of the lower part of the forearm and hand, was perceptibly higher than that over corresponding areas of the right arm. A resume of the measurements that were made with a thermocouple is given in table 5.

Numerous measurements of the arterial blood pressure were made independently by two observers. The blood pressure in the right brachial artery, taken by means of a standard mercury manometer, averaged 114 mm of mercury systolic and 64 mm of mercury diastolic, that in the left brachial artery, 128 mm of mercury systolic and 54 mm of mercury diastolic. Digital occlusion of the left subclavian artery caused a rise, on the average, of 10 mm of mercury in the right brachial diastolic blood pressure, the systolic blood pressure remained unchanged. Compression of the right subclavian artery caused no change in the left brachial blood pressure. The femoral arterial blood pressures of the right and left legs were equal, the average of numerous readings was 112 mm of mercury systolic and 66 mm of mercury diastolic. The differential pressure sign of Hill and Rowlands⁴ was not elicited. Digital compression of the left subclavian artery

TABLE 6—Measurements of Capillary and Arteriolar Blood Pressures

Site of Measurement	Capillary Pressure		Arteriolar Pressure	
	Right, Mm Hg	Left, Mm Hg	Right, Mm Hg	Left, Mm Hg
Arm, upper portion	10	10	45	45
Forearm, lower portion	9	11	55	60
Sternum	11		48	

caused a rise in the femoral diastolic blood pressure of 12 to 18 mm of mercury. The blood pressure readings of the leg were made by means of a special cuff, 20 cm in width.

Measurements of the capillary and arteriolar blood pressure⁵ were made according to the method used by Lewis and Haynal⁶ and by Ellis and Weiss,⁷ all measurements being made with the closed capsule. A summary of the measurements is presented in table 6. Each figure represents the average of many observations made independently by two observers. There is no significant difference between the measurements made on the two arms. The results are normal and do not indicate diminution in the peripheral resistance of the cutaneous vessels.

4 Hill, L, and Rowlands, R. A. Systolic Blood Pressure (1) In Change of Posture, (2) In Cases of Aortic Regurgitation, *Heart* 3 219, 1912.

5 By capillary pressure is meant the pressure necessary to cause minimal distinct blanching of the skin by compression of subpapillary venules (Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C. The Dynamics of the Circulation in Coarctation [Stenosis of the Isthmus] of the Aorta of the Adult Type, *Arch Int Med* 47 811 [May] 1931).

6 Lewis, T, and Haynal, I. Observations Relating to the Tone of the Minute Vessels of the Human Skin, with Remarks upon and Illustrations of Measurements of Pressure Within These Vessels, *Heart* 14 177, 1928.

7 Ellis, L. B., and Weiss, S. The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, *J Clin Investigation* 8 47, 1929.

The venous pressures in the right and left antecubital veins were measured according to the direct venipuncture method of Moritz and Tabora⁸ The corrected results of several measurements of the venous pressure in the right arm averaged 102 cm of water, in the left arm, 238 cm of water

The bradycardiac reaction was tested The ventricular rate under resting conditions averaged 84 beats per minute Digital compression of the left subclavian artery was followed by immediate lowering of the ventricular rate to approximately 68 beats per minute The time interval between compression of the vessel and the onset of slowing in rate was measured by sudden application of pressure to the upper part of the left arm by means of a large pressure bottle while a continuous electrocardiographic tracing was taken These observations were repeated on several occasions The decrease in ventricular rate occurred

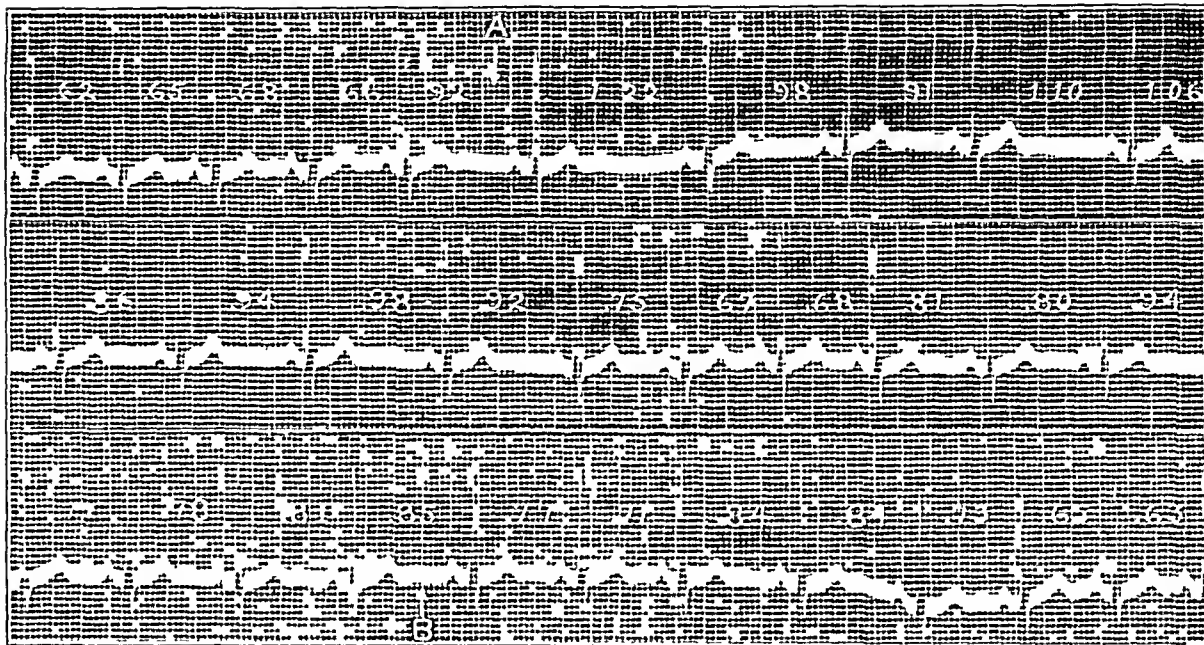


Fig 4—Electrocardiographic tracing illustrating the bradycardiac reaction produced by sudden application of pressure to the upper part of the left arm The pressure was applied at (A) and discontinued at (B) Slowing of the ventricular rate is evident in the first cardiac cycle following the application of pressure A secondary slight quickening in rate occurs after the first 10 beats The R-R intervals are indicated in seconds

as early as 0.09 seconds after the application of pressure In practically all instances, the slowing was evident in the first cycle following the application of pressure (fig 4) The lowering in ventricular rate was most pronounced immediately after pressure into the armlet, a secondary slight quickening in rate frequently occurring after the first ten or twelve beats No change in the contour of the complexes was observed

8 Moritz, F, and Tabora, D Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch f klin Med* 98 475, 1910

The volume of the blood and of the plasma were measured by the brilliant vital red dye method used by Thompson⁹ The results are presented in table 7, and are within the limits of normal

Duplicate measurements were made of the oxygen content and capacity of blood from the right radial artery, right antecubital vein, left radial artery and left antecubital vein The Van Slyke-Neill manometric apparatus was used The results are presented in table 8

Measurements of the velocity of blood flow were made by means of the radioactive method¹⁰ After the radioactive substance was injected into the antecubital vein, the time necessary for the substance to traverse the veins to the right auricle, as well as the time necessary for the substance to pass through the pulmonary

TABLE 7—*Measurements of Blood and Plasma Volume*

	Average Normal Values, Cc	Observed Values, Cc
Total plasma volume	3,550	2,482
Total blood volume	6,035	4,140
Plasma volume per kilogram	50	43
Blood volume per kilogram	85	72

TABLE 8—*Blood Gas Measurements*

Source of Blood	Oxygen Content		Oxygen Capacity		Percentage Saturation		Arteriovenous Oxygen Difference	
	Right, per Cent by Volume	Left, per Cent by Volume	Right, per Cent by Volume	Left, per Cent by Volume	Right, per Cent by Volume	Left, per Cent by Volume	Right, per Cent by Volume	Left, per Cent by Volume
	17.3	17.1	18.0	18.1	96	95	3.0	0
Radial artery								
Antecubital vein	14.3	17.1	17.7	18.2	81	94		

TABLE 9—*Measurements of Velocity of Blood Flow*

Site of Injection	Arm to Heart Time, Seconds	Pulmonary Circulation Time, Seconds
Right antecubital vein	7.5	9.0
Left antecubital vein	1.5	8.5

circulation, was measured¹¹ A summary of the measurements is presented in table 9 The pulse rate at the time of the measurements was 75, it was not

9 Thompson, W O Studies in Blood Volume I The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, *J Clin Investigation* 2 477, 1926

10 Blumgart, H L, and Yens, O C Studies on the Velocity of Blood Flow I The Method Utilized, *J Clin Investigation* 4 1, 1927 Blumgart, H L, and Weiss S Studies on the Velocity of Blood Flow II The Velocity of Blood Flow in Normal Resting Individuals, and a Critique of the Method Used, *ibid* 4 15, 1927

11 Blumgart H L and Weiss, S Studies on the Velocity of Blood Flow VII The Pulmonary Circulation Time in Normal Resting Individuals, *J Clin Investigation* 4 399, 1927

significantly altered by the procedure. The venous pressure in the right arm at the time of the injection into the vein of that arm was equivalent to 11.5 cm of water, the venous pressure in the left arm at the time of the injection into the vein of that limb was 23.6 cm.

The volume flow of blood per minute through the lungs (cardiac volume output per minute) was measured by the acetylene method of Grollman¹² both before and during occlusion of the vessels of the left arm. A summary of the measurements is presented in table 10. The flow before occlusion was 2.7 liters per minute, during occlusion, 2.9 liters per minute. The absence of any change may well have been due to the inapplicability of this type of method in the presence of free arteriovenous communication, the abnormally rapid return of blood¹³ from the left arm, as shown by the velocity of studies of blood flow, probably introduces an appreciable error. The measurements made while the left brachial artery was occluded may be regarded with greater confidence. They are practically within the limits of normal as observed by Grollman¹⁴.

The tourniquet test was made as follows. With the patient in the supine position and the arm held upright to facilitate venous return, the blood supply to each arm was suddenly interrupted by means of a pneumatic cuff. When the arm was

TABLE 10—Measurements of Cardiac Volume Output per Minute

	Oxygen Consumption, Cc per Minute	Arteriovenous Oxygen Difference, Cc per Liter of Blood	Cardiac Minute Volume Output	
			Total, Liters	Per Square Meter of Body Surface, Liters
Without occlusion of arteries of left arm	187	70	2.7	1.7
With occlusion of arteries of left arm	187	66	2.9	1.8

lowered to the horizontal position and the pressure then released, a flush appeared in the skin of the extremity after a short interval. Repeated observations showed that the time of appearance of the flush was identical in the two arms, the average being 2.8 seconds after release of the pressure in the left arm and 2.9 seconds in the right arm. These results are in accord with the measurements of arteriolar and capillary blood pressure, and indicate that the peripheral resistance in the cutaneous vessels of the two arms is equal and normal.

COMMENT

Detailed study of uncommon disease states is important particularly for two reasons. 1. The rarity of a condition and consequent lack of adequate information may lead to faulty diagnosis and treatment.

12 Grollman, A. Determination of Cardiac Output of Man by Use of Acetylene, *Am J Physiol* **88** 432, 1929.

13 Blumgart, H. L., and Weiss, S. Studies on the Velocity of Blood Flow. X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, *J Clin Investigation* **5** 379, 1928.

14 Grollman, A. Physiological Variations in the Cardiac Output of Man. VI. The Value of the Cardiac Output of the Normal Individual in the Basal Resting Condition, *Am J Physiol* **90** 210, 1929.

2 Pathologic abnormalities frequently provide an opportunity to study in isolated form certain mechanisms that increase our understanding of common conditions. The study of hemangiectatic hypertrophy reported here exemplifies both of these points. Lack of appreciation of the meaning of some of the clinical signs had led to fruitless surgical intervention at a point remote from the actual site of the lesion, the present detailed study of the peripheral blood flow has led to a fuller understanding of certain vascular phenomena that occur more commonly in other disease states.

The general manifestations of abnormally free arteriovenous communication observed in our patient may be considered conveniently under the following six headings:

1 *Arterial Blood Pressure*—Taking the pressure in the right brachial artery as an index of the general arterial pressure, the systolic pressure of 114 mm. of mercury may be considered normal, the diastolic pressure of 64 mm. of mercury was somewhat below normal. Lowering of the diastolic pressure is frequently more pronounced in cases of direct arteriovenous anastomosis with large fistulas, and is due to leakage of blood through the abnormal opening during diastole. The effect in our patient of the abnormal leakage of blood from arteries to veins on the general diastolic arterial pressure is shown by the fact that closing the left subclavian artery repeatedly caused a rise in the right brachial diastolic pressure, the average increase being 10 mm. of mercury. The increase observed in femoral diastolic blood pressure when the left subclavian artery was occluded is of similar significance. Compression of the right subclavian artery, on the other hand, did not affect the left brachial diastolic blood pressure.

In the left brachial artery the systolic blood pressure averaged 14 mm. of mercury higher, and the diastolic blood pressure, 6 mm. of mercury lower than in the right brachial artery. Both the elevated systolic pressure and the lowered diastolic pressure in the left arm were a direct expression of the local anatomic conditions. The lowering of the diastolic blood pressure in the left arm below that of the rest of the body was due to the proximity of the leakage of blood from artery to vein. At first glance, the relatively high left brachial systolic blood pressure appears strange, if the arteriovenous communications were proximal to the brachial artery, the abnormal leakage should cause a lowering in pressure, while if the abnormal communications were distal to the brachial artery, the blood pressure might not be affected. The locally elevated systolic blood pressure in the left arm may be explained, however, by the following considerations. The arterial pressure is highest in the larger trunks, such as the aorta, and undergoes diminution in the smaller vessels according to the resistance offered by their

decrease in caliber William Hunter,¹⁵ in 1762, and other observers¹⁶ since that time noted that arteries proximal to arteriovenous communications are dilated and therefore offer less frictional resistance The systolic pressure in a dilated peripheral artery consequently approximates more nearly the pressure existing in the larger central trunks In our patient the left brachial artery was obviously dilated and the left subclavian artery probably had undergone a similar change, since its pulsation prominently encroached on the left supraclavicular fossa The locally elevated systolic blood pressure in the left brachial artery is thus accounted for

2 *Bradycardiac Reaction*—Obliteration of abnormal arteriovenous communications or occlusion of the principal arteries leading to such communications causes a slowing of the heart rate, the degree of slowing is related to the amount of blood passing through such openings This phenomenon, as pointed out by Dean Lewis¹⁷ was first described by Nicoladoni¹⁸ in 1875 and by Israel¹⁹ in 1877 In our patient, digital compression of the left subclavian artery or application of pressure about the upper part of the left arm produced an abrupt fall in the heart rate the average decrease being 16 beats per minute A slight secondary increase in ventricular rate was noted during maintenance of the compression The extraordinarily brief interval between arterial occlusion and the bradycardiac reaction is in accord with evidence that the reaction is mediated through a reflex nerve mechanism Lewis and Drury,²⁰ and Nanu, Alexandrescu-Dersca and Lazeanu²¹ were able to abolish the bradycardiac reaction by atropinization

3 *Elevation in Venous Pressure*—In our subject, the venous pressure in the affected arm was greatly elevated, while the general venous pressure of the body, as gaged by the pressure in the right

15 Hunter, W Further Observations upon a Particular Species of Aneurysm, *Med Obs Soc Phys* **2** 390, 1762

16 Reid, M R The Effect of Arteriovenous Fistula upon the Heart and Blood-Vessels An Experimental and Clinical Study, *Bull Johns Hopkins Hosp* **31** 43, 1920 Callander, C L Study of Arterio-Venous Fistula with an Analysis of 447 Cases, *Johns Hopkins Hosp Rep* **19** 259, 1920

17 Lewis (footnote 2, third reference)

18 Nicoladoni Phlebarteriektasie der oberen Extremitat, *Arch f klin Chir* **18** 252, 1875

19 Israel, J Angiektasie im Stromgebiete der Arteria tibialis anterior, *Arch f klin Chir* **21** 109, 1877

20 Lewis, T, and Drury, A N Observations Relating to Arterio-Venous Aneurism I Circulatory Manifestations in Clinical Cases with Particular Reference to the Arterial Phenomena of Aortic Regurgitation, *Heart* **10** 301, 1923

21 Nanu, I, Alexandrescu-Dersca, C, and Lazeanu, E Les troubles cardiaques consecutifs aux anevrismes arterio-veineux, *Arch d mal du coeur* **15** 829 1922

antecubital vein, was within the upper limits of normal. Local elevation of the venous pressure in the vicinity of abnormal arteriovenous anastomosis was observed by Lewis and Drury,²² they also noted that the general venous pressure of the body was within the limits of normal. In the absence of evidence of venous obstruction in the left arm of our patient and in the absence of myocardial insufficiency, one must assume that the increased pressure in the veins of the left arm was due to a leakage of arterial pressure through the abnormal artery to vein communication. The elevated venous pressure in the left arm did not affect the general venous pressure in the rest of the body, repeated observations before and again during compression of the left subclavian artery showed no variation in the venous pressure readings of the right arm.

4 *Thrills and Murmurs in Peripheral Vessels*—Systolic and diastolic murmurs and thrills were evident over the subclavian and brachial vessels. These signs are evidence of abnormal arteriovenous communications.²³ The pathologic physiology of these signs and their significance in the diagnosis of the exact site and nature of the abnormal arteriovenous communication will be discussed.

5 *Systolic Venous Pulsation*—With the hand of the left arm 6.5 cm. below the level of the right auricle, systolic pulsation of the veins of the back of the hand were plainly visible. This finding was interpreted as additional evidence of free arteriovenous communication.

6 *Blood Gas Measurements*—The oxygen content of blood from the antecubital vein of the right arm was 3 per cent by volume less than that of blood from the right radial artery. This difference in oxygen content is within the limits of normal. There was no significant difference in the oxygen content of the blood from the left radial artery and that from the left antecubital vein (table 8). The arterial nature of the venous blood of the left arm indicates a conspicuously increased rate of flow through capillary vessels or a flow of blood from artery to vein which is relatively direct so that little opportunity is afforded for the giving-off of oxygen. At least a significant part of the abnormal flow from artery to vein was probably transported through dilated capillaries, for otherwise it is difficult to understand such phenomena as the increased growth of the affected parts.

We are unable to state the exact degree of increase in blood flow through the left upper extremity. The relatively moderate rise in general diastolic blood pressure of the body following occlusion of the abnormally dilated vessels, the absence of any change in the cardiac outlines after obliteration of the arterial leakage and the absence of

22 Lewis and Drury (footnote 20, cases 1 and 2)

23 Callander (footnote 16, reference 2)

cardiac hypertrophy indicate, however, that the amount of blood shunted through the dilated channels, while considerable, did not add greatly to the total blood flow of the body

Diagnosis of Site and Nature of the Arteriovenous Communication—The phenomena described in the foregoing paragraphs are the result of abnormally free communication between the arterial and venous systems. They do not denote whether the artery and vein communicate by direct anastomosis or by intermediate vascular plexuses. The mechanism of production of the murmurs and thrills in the peripheral vessels and the direction of transmission of these signs differ so widely from similar phenomena observed more commonly in cardiovascular disease that detailed study is necessary for accurate localization of the site of the lesion. In point of fact, the presence of thrills and murmurs in the brachial and subclavian vessels of our patient had led to a mistaken diagnosis of arteriovenous aneurysm and fruitless surgical intervention. We were inclined to make the same diagnosis after our first superficial examination but hesitated because of certain phenomena that were not in accord with this view of the condition. These phenomena were as follows:

1 *Direction of venous blood flow*. By stripping small segments of veins on the back of the left hand of their blood content and then releasing the distal portion, the veins were observed to fill immediately. When this procedure was repeated, but with release of the proximal portions first, filling took place very slowly. This observation indicated that the flow of venous blood was natural in its direction. If a direct artery to vein anastomosis had been present in the subclavian or brachial vessels, the flow of blood might have been reversed in some of the veins, or at least retrograde filling might have occurred. Such retrograde filling did in fact occur, but only when the arm was suspended at the side with the back of the hand 42 cm below the level of the right axilla. This finding was interpreted as due to incompetency of the valves of the veins, the situation under such circumstances being similar to that in varicose veins of the legs.

2 *Effect of arterial occlusion on venous pulsation and engorgement*. Compression of the left subclavian or of the left brachial artery caused disappearance of the pulsation and diminution in the engorgement of the veins of the back of the left hand. Compression of the radial and ulnar arteries singly was without this effect, but simultaneous compression of both vessels was immediately followed by the disappearance of the pulsation of the veins and by the lessening of their engorgement. These observations suggested that the arteriovenous communication was at or distal to the site of the radial and ulnar artery

compression. If the communication had been proximal to this level, compression should have increased the arterial leakage and led to more prominent venous pulsation and increased venous filling.

This tentative localization of the arteriovenous communications was next tested more critically. A needle communicating with a manometer filled with a solution of sodium citrate was inserted into the left antecubital vein. The venous pressure at this time was equivalent to 21 cm of water. With the needle freely communicating with the lumen of the antecubital vein, pressure above arterial systolic was applied over the lower ends of the left radius and ulna. The venous pressure immediately decreased to 15.2 cm. When the pressure at the wrist was released, the venous pressure immediately rose to 20.3 cm. These measurements demonstrated that the main communications between artery and vein were in large part at or distal to the lower ends of the radius and ulna.

3 Effect of arterial occlusion on general diastolic blood pressure. A rise in general diastolic blood pressure on compression of the arteries in the left arm may likewise be regarded as an indication that the abnormal leakage of blood occurs at or distal to the point of compression. This phenomenon may consequently be utilized as a test for localizing the site of the lesion. Artery compression distal to the site of the abnormal artery to vein communication would be either without effect, or, by favoring the leakage of blood into the veins would cause, instead of a rise, a further lowering in general diastolic blood pressure. The effect on the general arterial blood pressure as gaged by measurements of the right brachial systolic and diastolic pressures was observed, accordingly, after compression of the vessels at the mid-portion of the left arm and forearm. A definite rise in the diastolic pressure was uniformly elicited. A similar increase was produced by compression at the lower ends of the radius and ulna by means of a pneumatic cuff. The rise in diastolic blood pressure after compression at the mid-arm, mid-forearm and lower ends of the radius and ulna was as great as that produced by digital occlusion of the left subclavian artery. Since the magnitude of the rise in diastolic pressure is closely related to the amount of decrease in arterial blood leakage, these observations suggest that the principal abnormal artery to vein communications in our subject were at or below the level of the wrist.

4 Bradycardiac reaction. The lowering of the ventricular rate caused by compression of the left subclavian artery was due to cessation of the abnormal leakage of arterial blood into the veins. The slowing in the ventricular rate on the compression of an artery signifies that the abnormal arteriovenous communication lies in the segment of artery compressed or in its peripheral continuations. Accordingly, suc-

cessive measurements of the ventricular rate were made after obliteration of the vessels at the middle upper part of the arm and at the middle portion of the forearm by means of a pneumatic cuff. Repeated observations uniformly showed a fall of from 13 to 20 beats per minute in the ventricular rate. Simultaneous digital compression of the radial and ulnar arteries just above the wrist showed a similar lowering of the heart rate, again indicating that the principal abnormal anastomoses were either at or distal to the wrist.

5 Site of greatest increase in blood flow. Measurements of the actual volume of blood flow in various portions of the arm are not practicable. One would expect, however, that the greatest degree of hypertrophy and the greatest increase in skin temperature would occur in those regions where blood flow was most conspicuously increased. Linear measurements of the bones (table 1) and volume measurements of the hands, forearms and arms (table 4) showed the greatest changes evident in the left hand and left forearm. These measurements do not disclose whether the predominant changes in the forearm occur in its upper or lower portions. It is significant, however, that the measurements of skin temperature (table 5) which allow of more accurate localization, showed the greatest increase over the left hand and the lower part of the left forearm, and that the only bones that showed abnormal erosions were the middle phalanx of the left middle finger and the proximal phalanges of the left middle and ring fingers. These grooves were probably due to pressure atrophy caused by vigorous pulsation of abnormally dilated vessels;²⁴ this phenomenon is similar to the erosion of ribs observed in patients with coarctation of the aorta.²⁵ Although the aforementioned considerations indicate that the principal abnormal artery to vein leakage occurred at the wrist and in the hand, the lesion was probably not sharply demarcated but may have involved, to some extent, the middle and upper parts of the forearm. Evidence of the latter was suggested by the presence of cutaneous angiomata over these regions.

6 Observations on the arterial murmur and thrills. The systolic murmur and thrill over the left subclavian artery and over the left brachial artery were readily understandable on the basis of abnormal communications in the metacarpus and carpus. Duroziez' sign and

24 Ernstene, A. C., and Robins, S. A. The Roentgenologic Diagnosis of Stenosis of the Descending Arch (Coarctation) of the Aorta, *Am J Roentgenol* **25** 243, 1931.

25 Railsback, O. C., and Dock, W. Erosion of the Ribs Due to Stenosis of the Isthmus (Coarctation) of the Aorta, *Radiology* **12** 58, 1929. Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C. The Dynamics of the Circulation in Coarctation (Stenosis of the Isthmus) of the Aorta of the Adult Type. Relation to Essential Hypertension, *Arch Int Med* **47** 806 (May) 1931.

the diastolic thrill over these vessels were not so readily explicable. Occurring frequently in aortic regurgitation, Duroziez' sign is commonly attributed to a retrograde flow of blood during diastole. A diastolic reflux of blood in our patient could be hypothecated only if the abnormal arteriovenous communication were central to the site where the diastolic murmur and thrill were elicited. If the abnormal communication were thus centrally situated, compression of the brachial or radial and ulnar arteries would favor diastolic backward flow of blood toward the site of leakage, and would intensify the diastolic murmur and thrill. However, when the brachial artery was occluded by digital compression while a second observer applied a stethoscope over the subclavian vessels, the diastolic and systolic murmurs and thrills over the latter vessels completely disappeared. Digital compression of the radial artery alone or of the ulnar artery alone conspicuously diminished the murmurs and thrills, but these signs did not disappear until both vessels were occluded simultaneously. Application of pressure over the lower ends of the radius and ulna by means of the blood pressure cuff likewise effected the disappearance of the murmurs and thrills over the subclavian and brachial vessels.

The degree of compression necessary to cause disappearance of Duroziez' sign was tested by applying the blood pressure cuff to the middle of the forearm and placing the stethoscope over the brachial artery in the antecubital space. As the pressure within the cuff was raised, conspicuous diminution of Duroziez' sign occurred at 52 mm of mercury, complete disappearance occurred at 58 mm of mercury.

We were therefore forced to the somewhat surprising conclusion that both the systolic and diastolic murmurs and the thrills over the subclavian, brachial, radial and ulnar vessels were due to abnormally increased forward blood flow not only during systole but also during diastole, and that the increased blood flow occurred mainly because of abnormally dilated communications between the arteries and the veins about the wrist and the hand.

The pathologic physiology of Duroziez' sign has been studied in a variety of conditions, and its importance in differentiating aortic regurgitation from other conditions with similar peripheral phenomena will be the subject of a communication in the near future.

SUMMARY AND CONCLUSIONS

1. A case of hemangiectatic hypertrophy and congenital phlebarteriectasis has been studied clinically. As a result of the observations made criteria for the diagnosis of the condition have been established.

2. The left arm was conspicuously larger than the right, the blood flow through the left upper extremity was considerably increased, but the volume output of blood per minute from the heart and the velocity

of blood flow through the lungs were normal. The velocity of blood flow in the left arm was far greater than that in the right arm.

3 The so-called diagnostic signs of arteriovenous aneurysm are not diagnostic of arteriovenous aneurysm but are rather to be regarded as signs of free arteriovenous communication. The exact nature and site of the communication must be determined by further study.

4 The following signs may be regarded as manifestations of free artery to vein communication, they do not denote whether the artery and vein communicate by direct anastomosis or by intermediate vascular plexuses: (a) increase in pulse pressure in the affected part due to elevation in the systolic and reduction in the diastolic blood pressure; (b) lowering of the general diastolic arterial pressure of the body; (c) increase in venous pressure in the affected veins and their tributaries without the general venous pressure of the body necessarily being affected; (d) capillary pulsation; (e) raised ventricular rate; (f) normal or increased output of blood from the heart; (g) normal or increased size of the heart; (h) abnormally high oxygen content of the venous blood of the affected part; (i) elevation in the temperature of the skin of the region in which the abnormal communication is situated; and (j) thrills and murmurs over the site of the abnormal communication and over the arteries leading to the lesion.

5 If after an artery is occluded the ventricular rate slows, the general diastolic blood pressure of the body rises, a lessening of venous engorgement of the affected part occurs and the peripheral murmurs and thrills disappear, the abnormal artery to vein leakage lies in the segment of artery compressed or in its peripheral continuation.

6 The signs of multiple free communications characteristic of hemangiectatic hypertrophy and congenital phlebarteriectasis that distinguish this condition from the direct anastomosis of arteriovenous aneurysm are as follows:

(a) There are usually several or numerous dilated arteries leading to the site of phlebarteriectasis, there is generally but one dilated arterial trunk leading to an arteriovenous aneurysm.

(b) Systolic venous pulsations are transmitted away from the periphery in congenital phlebarteriectasis; they are transmitted toward the periphery as well as centrally in arteriovenous aneurysm.

(c) Increased growth of the region in which the abnormal communications are situated favors the diagnosis of phlebarteriectasis rather than arteriovenous aneurysm.

THE MAN-ENVIRONMENT UNIT AND PEPTIC ULCER^{*}

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Natural historians have always insisted that it is impossible to think of a living creature apart from its environment. Indeed, the two are so intimately joined that it is no easy task to decide, for example, at what stage oxygen from the surrounding air fuses as oxyhemoglobin with the structure of the organism, or when ingested carbohydrate becomes vitalized in the energy productions of muscle. Consequently, the investigation of a human being's constitution must include all the gross and subtle details of his environment—it becomes in effect a study of the "man-environment unit." The problem would perhaps be easier if the palpable universe comprised man's only envelop. But because of his imaginative faculty, his phantasy life, another vast imponderable yet entirely personal universe supplies an equally complex and poignant environment to which he must likewise make adjustment. To the pressure of the physical world he responds in general with consciously directed muscles. Such muscles are chiefly concerned with the life of gross or spatial relation to environment. The other variety of muscle, nonstriated and not under conscious control, carries out the vital processes supporting the life of inner existence and procreation. But this type of contractile tissue is strongly influenced by emotions. Yet it is not necessary that the emotions be perceived in consciousness to be effective in modifying the function of organs equipped with smooth muscle. Ordinarily, if the organism is in good emotional equilibrium, the body machinery moves easily at its work, quite automatically and unnoticed by the individual. But if there is a disturbance, no matter how minute, of the balance between the human animal and either of its two universes, signs of that disturbance are immediately apparent. Consequently, we may accept the thesis that disease is simply the expression of maladjustment between organism and surroundings, an overthrow of the delicate structure termed the "man-environment unit."

Gastro-enterology, dealing with the stomach and intestines, is concerned with vital apparatus which is perhaps more than any other

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physiologic system exposed to blows from both ponderable and imponderable worlds. Physical, chemical and thermal onslaughts alternate with the rapid fire of emotions, such as fear, anger, jealousy and sexual confusions. Yet no two stomachs and no two intestinal tracts react similarly to any of these menaces. This is because the gastrointestinal tract is not the man, the whole man is the digestive mechanism, and as the whole man responds to the pressure of the whole environment, so will any of his parts respond—for each cell and system within him is stamped indelibly with his special mark. This special mark has been called the personality. It was for this reason, doubtless, that we found the peptic ulcer race so well adapted to our studies in constitution. The methods to which reference will be made and the descriptions, interpretations and conclusions are applicable in principle to the subjects of any illness. However, they are, in this communication, based on observations of what we have called the peptic ulcer race. We are aware that the use of the term race, with such a connotation, is unacceptable to some critics of the work. But if, in this connection, the word is deprived of its ethnological significance, it is at least etymologically and by derivation permissible.

While in our previous studies the plan of recording observations was carried out on the four panels of personality, anatomy, physiology, psychology and immunity, we have found it simpler for our present purpose to discuss the material under three headings, namely, genetic, anthropomorphic and anthropopsychic.

GENETIC STUDIES

The genetic studies have not been made primarily to display a disease tendency, but rather to uncover trends in the constitution of the family, just as they have been studied in the individual. With the emergence of the total personality as an essential factor in the causation of disease, it becomes increasingly necessary to observe the elements from which it arises. The physician cannot gain complete understanding of his patient if the more important aspects of the latter's heredity are omitted from the study. Often, also, the patient throws much light on his own psychologic patterns and conflicts as he discusses the members of his family, their traits and habits, their adjustment to environment and his relationship with them.

The hereditary influences play the basic rôle in the final determination of the man, his morphology, his psychology, his strengths and his weaknesses in all the systems of the body. But these inherent values are strongly conditioned by his surroundings. The finished individual, the phenotype, is therefore the up-to-the-moment resultant of the interplay between inherited qualities and the modifying influences from the world about him. For example, it might be imagined that four brothers of

the same fraternity have the same general inherited weakness of the gastro-intestinal tract. In number one, there is also a psychic instability, and the nervous response to slight stimuli may affect the visceral nervous system so adversely that he early finds himself incapacitated by ulcer of the stomach. Number two has a more stable nervous system and yet is subjected to the vicissitudes of life so forcibly that the deleterious effect is felt in the gastro-intestinal tract, though perhaps not so severely as in number one. Number three may have a poor nervous make-up, yet at the same time his adjustment to the environment may be so good that the weakness remains undisclosed. Number four may have both a good nervous system and environmental adaptation and like number three, may remain well.

The genetic studies have embraced the following points: racial extraction, morphologic types, disease history, sex distribution and psychologic make-up. Such a graphic description of the family brings into much clearer relief the characteristics of the patient. In the disease and psychologic pattern the patient is often liable to project his own symptoms on the various members of the family, hence the necessity of interviewing other members besides the patient. Histories of thirty-two ulcer families and thirty-two gallbladder families have been used for this study. To draw conclusions from so small a series is obviously unwise. Yet the close approximation of our findings in respect to disease frequency and other studies of greater numbers gives confidence in the validity of the general trends displayed in the "family history." Naturally disease overlappings are frequently found, and no family presents a homogeneous pattern. However, when these two groups of families are placed side by side the differences stand out quite as clearly as do the differences in the individual patients of the two groups.

Sex Distribution—The ulcer families are represented by 26 male patients and 6 female patients, and the gallbladder families by 5 male patients and 27 female patients. No sex selection was made in taking the histories, so long as the patient was able to give intelligent cooperation. In the members of the ulcer patient's immediate fraternity, a sex distribution in the ratio of 138 males to 100 females is found, while the gallbladder families present quite the opposite picture of 100 males to 130 females. There is, then, a tendency for the ulcer families to produce a preponderance of males and the gallbladder families a preponderance of females.

Morphology—In general terms a description of the habitus of members of the family was elicited. The terms slender, medium, stocky and stout were employed. The ulcer families reported 75 per cent of the brothers and sisters of the patient as slender or medium build while the gallbladder families reported 54 per cent of the immediate members of

the patient's fraternity as stocky or stout. Seventy per cent of the fathers of patients with ulcers were described as medium or slender build, and only 30 per cent as stocky or stout. Of the fathers of patients with gallbladder disease, 55 per cent were described as slender or medium and 45 per cent as stocky or stout. The mothers of patients with ulcers, were reported as 55 per cent thin and 45 per cent stout, while just the opposite picture was found among the mothers of patients with gallbladder diseases, with 55 per cent stocky and 45 per cent thin. The findings show that the slender and the medium build are in the majority in the ulcer families and the stocky or stout in the majority in the gallbladder families.

Disease Incidence—Peptic ulcer was found in 6 families, indefinite stomach trouble occurred in 13 additional families and cancer of the gastrointestinal tract in another family, a total of 20, or 62 per cent with a heredofamilial weakness of the gastro-intestinal tract. Ruhmann¹ found 48 per cent of 50 families with a similar hereditary history, Aschner² found 65.3 per cent and Spiegle³ found 61 per cent. Aschner reported that 15 per cent of the families of healthy persons gave such a history, Spiegle reported 15.5 per cent. Assuming that there is a hereditary influence, the tendency is in the form of a pathologic inferiority of the gastro-intestinal tract.

Ruhmann¹ pointed out that definite ulcer is more frequent among the sibs and descendants of the patient, and indefinite stomach trouble is commoner among the ascendants. The question arises as to the possibility that this fact may be due to more refined diagnosis nowadays and the closer familiarity of the patient with his own and the succeeding generation. Aschner² concluded from her studies of 120 ulcer families that the gene for stomach inferiority is a recessive, but is not sex-linked. She found that in cases in which both parents were affected, 50 per cent of the offspring were also affected. If one parent is sick and the other has a sick heredity, 25 per cent of the offspring are affected. If both parents are well but show a sick heredity, 10 per cent of the offspring are affected. The small number of families comprising our series hardly permits of such an analysis. After working over a long period with patients with ulcer, we have found it hard to conceive that a specific gene weakness is responsible for so complicated a disturbance of the vegetative nervous system as that which results

1 Ruhmann, W. *Der Ulcuskranke. Studien zur Konstitution und Symptomatik am gesamten Status bei chronischen Ulcus pepticum mit besonderer Berücksichtigung des vegetativen Nervensystems*, Berlin, S. Karger, 1926.

2 Aschner, B. *Ueber Konstitution und Vererbung bei Ulcus ventriculi und duodeni*, *Ztschr. f. d. ges. Anat.* **9** 6, 1923.

3 Spiegle, E. *Deutsches Arch. f. klin. Med.* **126** 45, 1918.

in lesions of the gastro-intestinal tract. Nor can we accept the condition as a recessive mendelian phenomenon in view of the variability of the external influences that may determine its expression.

Among the immediate members of the patient's fraternity, our studies show that 35 males to 1 female express gastro-intestinal weakness, exclusive of the patient. The mothers show the condition twice as often as do the fathers. Seven families gave a history of such weakness among the maternal collaterals and only one among the paternal collaterals. In this connection it should be stated that the maternal line is frequently better known to the patient than the paternal line. In all except one case the relatives with gastric symptoms were described as of slender or medium build. The gallbladder families show that in the members of the patient's fraternity, exclusive of the patient, indefinite digestive disturbances are three times more frequent in females than males. The condition occurs with about equal frequency in the paternal and maternal lines.

Tuberculosis was found in twelve ulcer families, or 37 per cent. Ruhmann¹ reported a 30 per cent incidence in his fifty families. The condition occurred twice as frequently in males as in females. Pneumonia was reported in 50 per cent of the ulcer families, and again this condition was found to be twice as frequent in males as in females. When it is recalled that the ulcer families are represented by twenty-six males and six females, the preponderance of male susceptibility to diseases within the zone of the pneumogastric nerve in these families is interesting.

Asthma occurred in eight, or 25 per cent, of both the ulcer and the gallbladder families. Diabetes occurred in only two ulcer families, as compared to seven gallbladder families. Gallstones were reported in two ulcer families, a mother was the subject in each case. This gives a gallstone incidence of 6 per cent as compared to 8 per cent found by Ruhmann¹. The gallbladder families reported eleven cases, or 34 per cent of gallstone. No cases of goiter were reported among the ulcer families, while the gallbladder families reported four cases. Arthritis was found in one ulcer family and in three gallbladder families.

Psychologic Make-Up—The study of the psychologic make-up of the families offers many difficulties. To extract from a patient a picture of the colorless personality of a brother, for example, is often an almost impossible task. Yet something may be gained from direct questioning about his schooling, occupation, stability in work, marriage, hobbies, interests and his reaction to any specific situation with which he would be likely to come in contact. To present this phase of the study statistically is obviously impossible. However, a perusal of sev-

eral selected histories will doubtless go far to show how strongly personality patterns are imprinted in the family

Schematic patterns of the families of the patients in the four cases in which analytic histories are given in this paper will be presented. They will be found in the anthropopsychic chapter together with the case histories. The charts display the main outlines of personality which are most typical and most often found in the ulcer families. Also, the disease display and morphologic aspects of the family members are noted.

Summary—The genetic studies may be summarized as follows:

1. There is a tendency for the ulcer families to produce a preponderance of males and the gallbladder families a preponderance of females.

2. Patients with ulcers are of families in which the long thin type predominates as contrasted to the gallbladder families in which the short thick type is in the majority.

3. There is definite evidence in the ulcer families of a heredofamilial weakness of the gastro-intestinal tract, 62 per cent of the families reporting such a history.

4. Gastro-intestinal weakness is three and one-half times more frequent among males than among females in these families, and almost without exception it is found in thin people. Males of these families are also much less resistant to other diseases in the zone of the pneumogastric nerve (tuberculosis and pneumonia) than are females.

5. Diseases of a catabolic nature occur more frequently in ulcer families, and anabolic disease more frequently in gallbladder families.

ANTHROPOMORPHIC STUDIES

The literature on peptic ulcer is filled with references and descriptions of the body build of such sufferers. There is general agreement that they belong to the so-called asthenic type. But, at this point, we must take exception to the use of the terms sthenic and asthenic, originally introduced by Stiller⁴ to describe certain inadequate human beings. Sthenic, from the Greek *σθένος*, means strength, and when used of man or animal connotes an energy producer. The term sthenic has, of late, been loosely used to signify the short thick-set type originally described by Hippocrates, just as its opposite, asthenic, is now applied to the long, thin variety. Now, so far as intensity and, indeed, duration of energy production are concerned, long slender people often surpass the thick-set. It is consequently misleading to designate mor-

⁴ Stiller, B. Die asthenische Konstitutionskrankheit, Stuttgart, Ferdinand Enke, 1907.

phology by a word that indicates physiologic quality. However, the term asthenic in this instance has been linked with the slender individual whose ponderal index (that is, the height-weight ratio) is consistently low. Aschner,² in a most comprehensive study of the subject, concluded that there is no typical ulcer habitus. Our observations do not support this finding, indeed they clearly envisage not only a physical and psychic type subject to this disease, but one so well defined that it is possible, almost without error, to determine from the individual's constitution whether the location of the ulcer is gastric or duodenal. The differences will be discussed later. Also in disagreement with Aschner, both Tscherning⁵ and Ruhmann¹ expressed the belief that patients with ulcers are found chiefly in the ranks of the linear types, with certain admixtures of the lateral. According to our observations, derived by both anthropometry and anthroposcopy from 125 cases, the peptic ulcer race is definitely composed of the linear, rather than the lateral, type of person. However, while they are slender and even in good health, presenting a consistently low ponderal index, they cannot properly be called asthenic. On the contrary, unless seriously depleted by the disease, they display an astounding amount of swiftly liberated, and often sustained, nervous force. This produces in many of them that quality of quick physical elasticity which bespeaks a high energy potential. Such an impression naturally gains vividness and color from the state of psychic or emotional tension. This aspect of the total personality will be dealt with later.

The facial design of members of the ulcer race is not so different from that of the general run of humanity as to make at first a striking impression. Yet when one has become familiar with its detailed characteristics, it is not difficult to recognize. In general, this face is broader in its upper half and tends to taper, rather sharply, to a small pointed chin. The eyes are separated by an interpupillary distance of from 60 to 62 mm, which is the average for the general population. But the relation between the interpupillary space and the facial diameter is the most satisfactory from the standpoint of appearance of all the disease groups. The eyes are neither too close together nor too far apart. The palpebral fissure is consistently wide, often enough to show the sclera above the iris. This character is especially interesting in view of other evidences of tension of the vegetative nervous system, which will be referred to subsequently. It doubtless accounts for the alert, watchful expression, which conveys a suggestion of continual apprehension mixed with defiance, common to the ulcer type when the person is in good health. But when the gastric symptoms are

⁵ Tscherning, R. Ueber die somatische und psychische Konstitution bei *Ulcus ventriculi*, Arch f Verdauungskr **31** 351, 1923

severe and the whole organism is reduced from the effects of indigestion and scant diet, then the wide eye slit produces the characteristic expression of exhaustion and despair with which every one is familiar. The defiant note has gone.

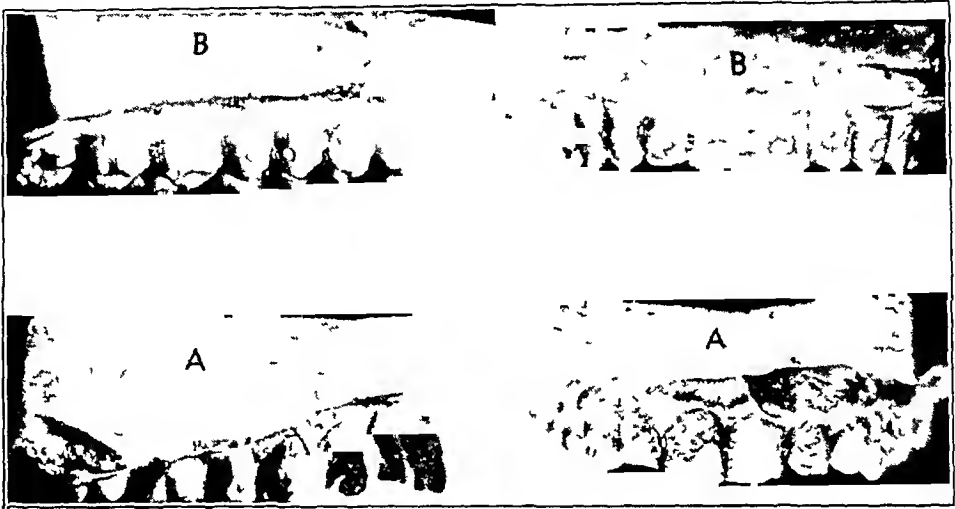


Fig 1—Lateral and front view of the upper jaw. *A*, ulcer, labial version of incisors and curving occlusion, *B*, gallbladder, vertical or lingual version. Straight occlusion. (From Draper, G., Dunn, H. L., and Seegal, D. *Studies in Human Constitution*, J. A. M. A. 82: 431 [Feb. 9] 1924.)

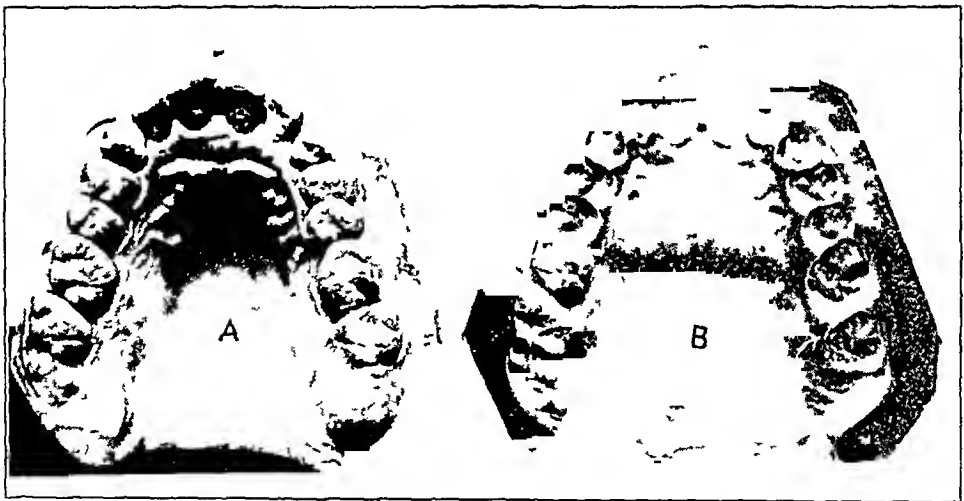


Fig 2—Palate view of the upper jaw. *A*, ulcer, pointed incisor arch, deep palate, forward slanting incisors, *B*, gallbladder, flat incisor arch, shallow palate, vertical insertion of incisors. (From Draper, Dunn and Seegal.)

Although the lower part of the face in general tends to be smaller than the upper, it presents significant details of structure in both the upper and the lower jaw. The dental ridge (figs 1 and 2) usually forms a U-shaped oval, and the vertical cross-section of the hard palate

shows an arch of similar design. The incisor teeth extend in slight labial version from the anterior alveolar margin. From this, the palatal arch sweeps up and back in a low slanting curve to the deepest part of the vault almost at the posterior edge of the bone. The teeth themselves are usually of clear pearly quality. The lateral incisors are definitely narrower than the central, the biting edge is sharp, and the profile curve of the bite line is waving, with low points at the molars and incisors. In the lower jaw (fig 3), the gonial angle (formed by the intersection of the posterior border of the ascending and the lower border of the horizontal ramus) averages 124 degrees, which falls well within the range for the general population (from 118 to 127 degrees). Clearly, then, this character is not significant in respect of the general population. But it gains immediate inter-disease group significance when compared with the 115 degree angle of the gallbladder people, and the

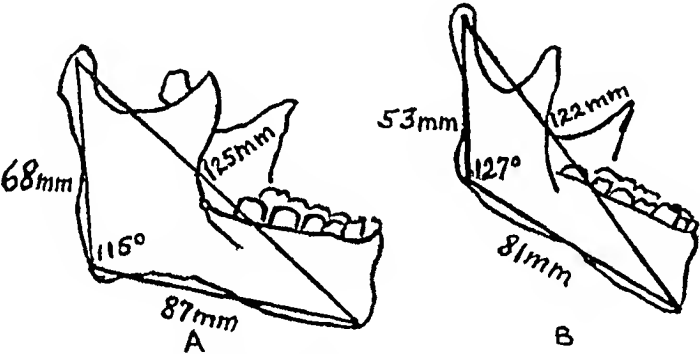


Fig 3—Diagram of the jaw types from the gallbladder (A) and the gastric ulcer (B) race. (Reproduced by courtesy of the Williams & Wilkins Company, Baltimore.)

130 degree angle of the people with acute rheumatism. The following tabulation shows some of the more important inter-disease differences.

	Peptic Ulcer Mean	Gallbladder Mean	Range for General Population
Ponderal index	32.2	44.0	33-41
Gonial angle	122.5°	115.0°	118-127°
Subcostal angle	44.5°	62.0°	35-60°
Anterior index, upper jaw	54.0	58.0	
Anterior-posterior chest diameter	200.0	222.0	190-220
Anterior-posterior diameter/chest length index	58.8	66.8	58-66
Lateral incisor/central incisor index	75.0	89.0	78-94
Hand index	45.8	47.2	44-48

From the standpoint of anthropometry, the significant features of the trunk and extremities are the somewhat low anterior posterior diameter-chest length index, narrow subcostal angle, relatively short arms and eunuchoidal trunk-extremity ratio. The hands are slender and long fingered, and the nails are narrow, long and laterally curved, and in the gastric group often display well marked lunulae. At this point it may be well to say that the duodenal cases present in general the same morphology, but almost every detail is slightly heavier or coarser. The trunk is thicker set, the subcostal angle is not so consistently narrow, and the extremities are less lanky and eunuchoidal.

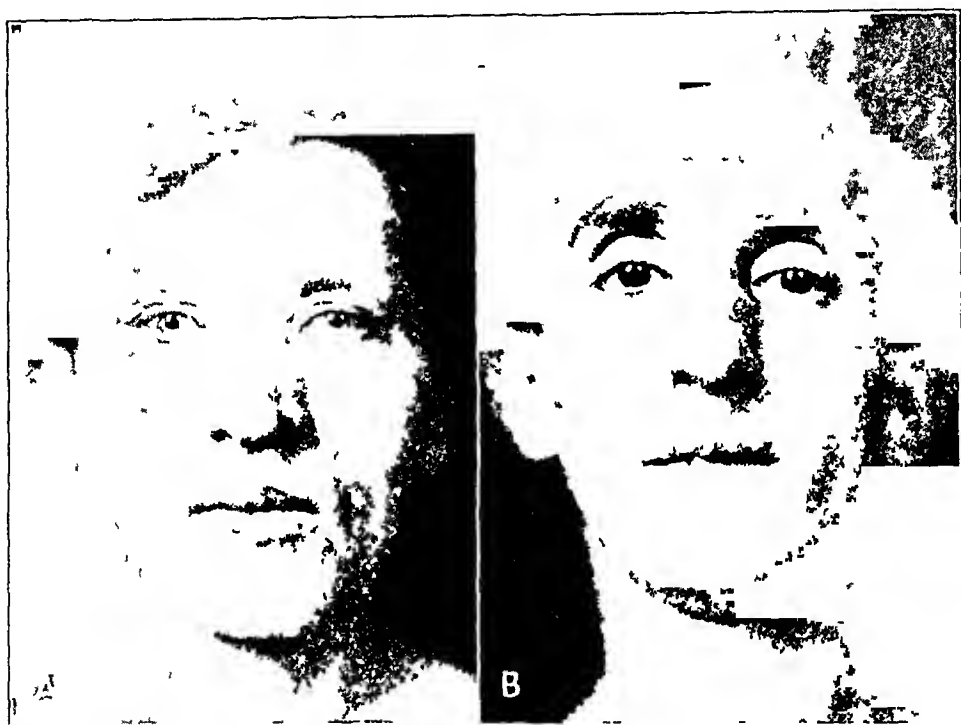


Fig 4—A, face view of a man with a duodenal ulcer. B, face view of a man with a gastric ulcer.

The hands are not so gracile, and the nails are flatter and squarer and show smaller or absent lunulae. The pilous system is usually not very strongly developed in either group. Though, in the males, the hair distribution follows generally the so-called masculine distribution, lightness of growth and occasional absences occur in zones that are characteristically bare in the female. The facial hair is almost always vigorous and abundant, especially in the gastric group. But in addition to the suggestion conveyed through the body hair, the body form displays numerous other subtle indications of this emphasis of the female component in the androgynous mosaic of these patients. Among these may be mentioned slightly sloping shoulders, more marked in the duodenal group, short arms and fulness over the trochanter region and

above the gluteal masses and the curve of the outer margin of the leg below the knee (figs 4 and 5)

There are a few instances in which both peptic ulcer and cholelithiasis occur in the same person St John⁶ reported 13 in a series

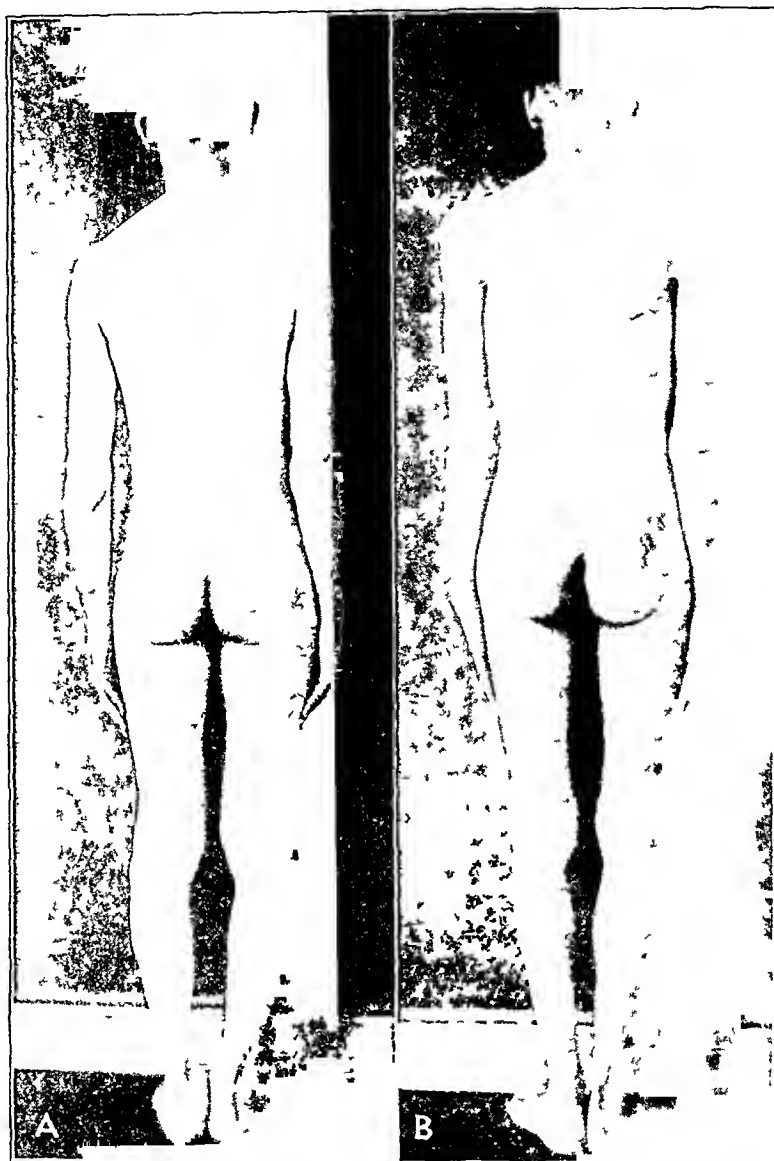


Fig 5—*A*, back view of a man with a duodenal ulcer *B*, back view of a man with a gastric ulcer

of 490 peptic ulcers Of these 13, the ulcer was duodenal in 11 cases, pyloric in 1 and gastric in 1 instance The 1 case in our series conformed morphologically to the other members of the uncomplicated duodenal group

⁶ St John, F B Unpublished report

ANTHROPOPSYCHIC STUDIES

In our previous studies⁷ of the psychologic panel, the chief emphasis seemed to fall on the exaggerated fear sense in the peptic ulcer race. The motor and psychomotor activity was found to be unusually high, and the patients were prone to swift and intense excitability. Their capacity for long-sustained effort is not great, they are of those whose intense activity is intermittent, because they are easily fatigued. Still they recover their energy promptly after short rest periods and the frequent ingestion of food. The direction of their interest and attention is generally outward, classic extroverts, who engage busily with the passing show. Beneath an outward manner of assurance, ready to

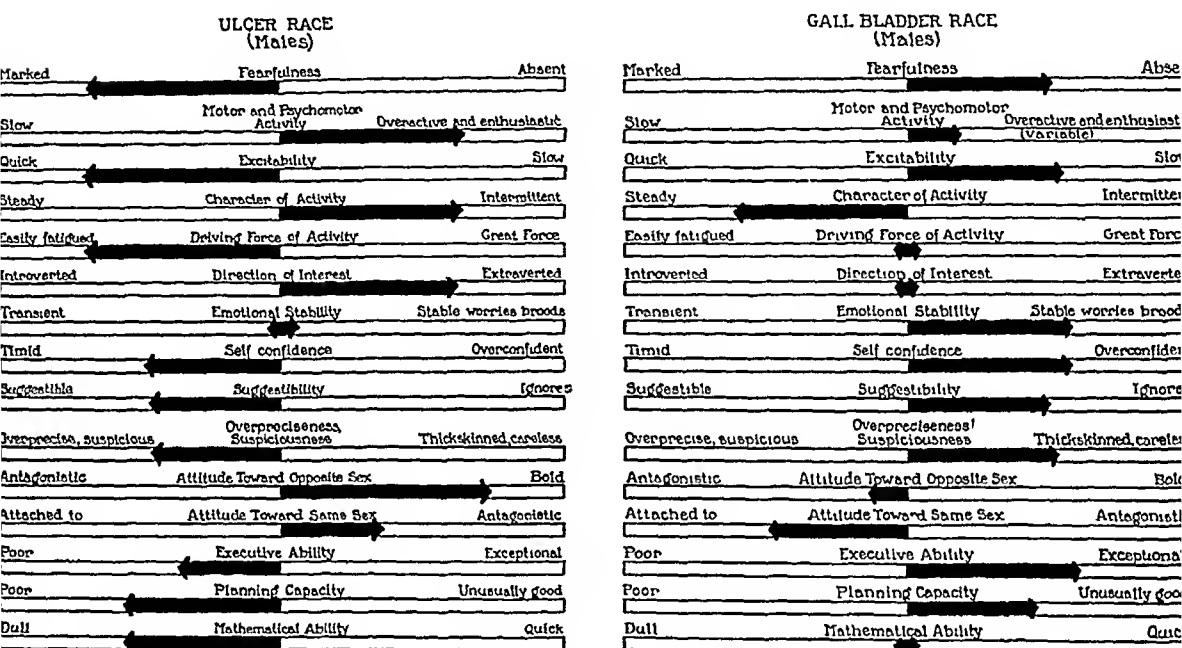


Fig. 6—Psychologic panels

seize any opportunity which offers, there is a latent timidity. This may be one cause at least for their tendency to overpreciseness in all they do and to be suspicious of people and situations. They are easily suggestible. In their relation to the opposite sex, the males are bold and eager and display an exaggerated heterosexual interest. Conversely, they show signs of antagonism toward their own sex. The females, on the other hand, have definitely diminished interest in erotic experience. All the orderly, more logical qualities, such as planning capacity and executive and mathematical ability, are not naturally highly developed in these mercurial people. Often, however, by a powerful compensatory effort they succeed in schooling themselves in executive work (figs. 6 and 7).

⁷ Draper, G., and McGraw, R. Studies in Human Constitution. V. The Psychological Panel, *Am J M Sc* 174:299, 1927.

In our original interpretation of the total personality of the peptic ulcer individual, we concluded that both on morphologic and on psychologic grounds maleness was the essential feature. Apparently this thesis was further supported by the statistics of sex incidence of the disease. It is true that some observers report more female cases than male, and that today in Germany peptic ulcer is believed to be more frequent in females than in males. However, more recent publications undoubtedly give precedence to men. Thus, St John⁶ reported in a series of 281 duodenal ulcers a sex ratio of 9 males to 2 females, among 87 pyloric ulcers, 5 males to 3 females and among 104 gastric ulcers, 3 males to 2 females. A further reference to this descending ratio will be made later.

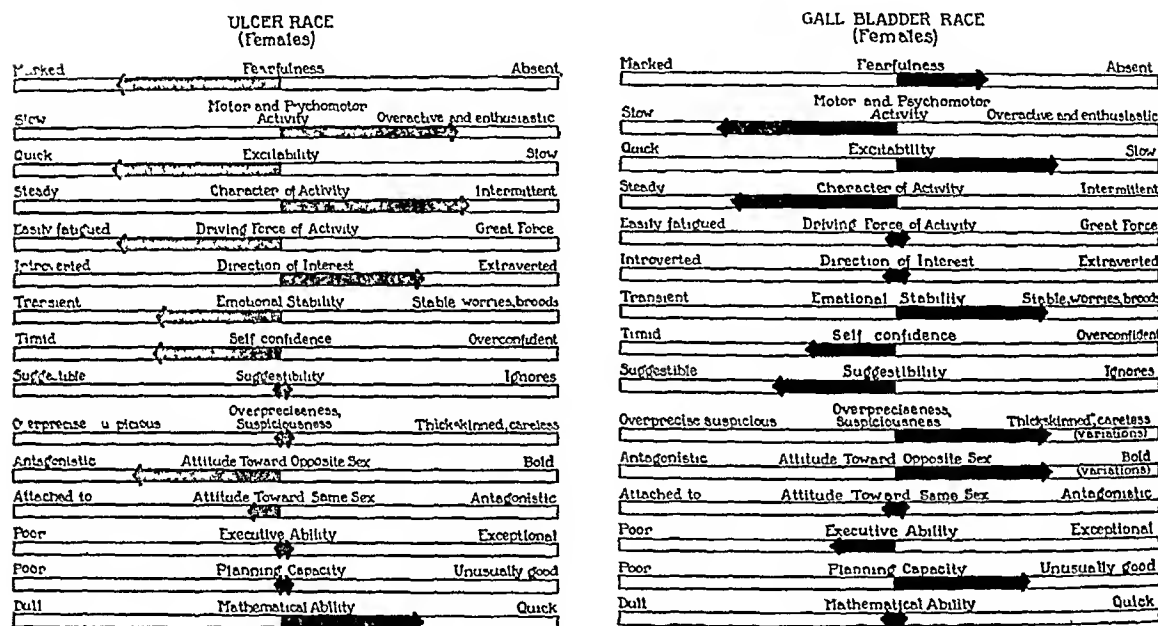


Fig 7—Psychologic panels

Recently, however, while reading Crile's⁸ paper on the subject of recurrent hyperthyroidism and recurrent peptic ulcer, certain questions arose concerning the validity of the male disease thesis which we have heretofore held. In that communication Crile pointed out that 60 per cent of patients with hyperthyroidism have digestive disturbances. He further called attention to the similarity of evidence of vegetative nervous system disturbance found both in patients with exophthalmic goiter and in those with peptic ulcer. Among these patients, for example, were widening of the palpebral fissure, fatigue, decrease of tissue and body fluid pH , sweating palms and the subjective feelings

⁸ Crile, G. W. Recurrent Hyperthyroidism, Recurrent Peptic Ulcer, Proc Inter-State Post-Grad M. Assemb., North America, October, 1929, p. 355.

of nervousness. He was able to show that when myxedema was produced, the acidity diminished. In five cases of peptic ulcer which had resisted medical and surgical treatment, he further demonstrated by resection of the left suprarenal gland and part of the thyroid, that the acidity could be reduced to normal. In addition to these observations of Crile, it is commonly known that exophthalmic goiter and hyperthyroidism are from six to eight times more frequent in women than in men. Similar suggestions are found in Simnitsky's⁹ work on the sympathetic nervous system. In view of these considerations, consequently, it would appear paradoxical that more men than women should be affected with ulcer. The only explanation for this paradox seemed to be in the fact of femaleness within the male.

This disclosure led us to reexamine the literature and our own case histories and observations. We soon began to see the evidences of emphasis on the feminine character of body build which have been referred to, and further to discover in the psychologic structure similar but more marked and important characters. The violent impetuous behavior that we had viewed objectively and supposed to be the demonstration of virility, on deeper psychologic investigation, turned out to be of quite a different nature. In the earlier literature on this subject of peptic ulcer, there are indications that a highly sensitive, feminine quality of temperament was recognized by certain observers. Thus, Gilles de la Tourette¹⁰ not only gathered statistics which showed in one series a ratio of 2 males to 1 female and in another series 1 male to 4 females, but in addition pointed out that there was a strong hysterical trend in the patients with ulcer and emphasized as a possible cause of ulcer the well known vasomotor and trophic disturbances of hysteria. Charcot¹¹ likewise suggested that the "crise noir" or vomiting of blood might sometimes be hysterical. In referring to this point nearly fifty years later, von Bergmann¹² declared that an ulcer often hides behind the "crise noir" of Charcot. This same author, summing up the now generally accepted belief that a strong emotional factor contributes to the cause of ulcer, pleaded for the most finely drawn anamnesis and what he termed the "subtile diagnose." He urged physicians not to be misled by the stolid men of the Holsteiner beneath which the tension of emotional conflict may be terrific.

9 Simnitsky, S. Weitere Beobachtungen zur Frage über die Bedeutung des Milieus in der Pathogenese der peptischen Geschwüre, *Klin. Wchnschr.* 6:991, 1927.

10 de la Tourette, Gilles. L'ulcère ronde et hystérie, *Semaine med.* 19:377, 1899.

11 Charcot, J. M. Leçons du mardi à la Salpêtrière, Paris, E. Lecrosnier & Babe, 1889, vol. 2, pp. 272 and 342.

12 von Bergmann, G. Die nervösen Erkrankungen des Magens, *Verhandl. d. Gesellsch. f. inn. Med.*, 1924, Kongr. 36, p. 168.

But it is the nature of this conflict that has interested us especially during the past two or three years. That fear is clearly an important element there is no doubt. Yet it is not always easy to connect a conscious fear with the gastric symptoms. Not infrequently, of course, an acute fear episode is closely associated with a violent gastric attack, hemorrhage or even perforation. Nevertheless, there is good reason to believe that the original formation of the ulcer occurred a long while before one of these serious events. Fear has not been recognized consciously, however, in the earlier stages of the malady, and, indeed, is usually denied vigorously by the patient. This situation is well illustrated by the case one of us reported last year of the public official whose hemorrhage occurred following a narrow escape from death by collision with a railroad train. This patient's ulcer had existed for some time prior to that nearly fatal event, its formation was related to his childhood and adolescent fear of humiliation because of unsuccessful competition with his younger brothers. Later on, after two years without symptoms and a continuous diminution in the size of the crater, as shown by roentgenograms, gastric symptoms returned temporarily when a fellow passenger at sea died, in a few hours, of perforation.

In other words, there seem to be two separate and independent sources of fear. One of these is subconscious and unrecognized by the patient. The anxiety that arises from this level has been at work over a long period. The other, consciously perceived, is formed by the menacing episode that threatens life, limb or ego. The former more chronic element of this double fear attack has engaged our interest, especially of late, because it appears to be almost part of the constitution itself.

In this connection it is of interest to refer to the work of Cannon¹³ on the autonomic nervous system. He remarked in his "Linacre Lecture"

Not only states of the external environment itself, but responses of the organism to situations in the external environment, are associated with disturbances of the internal environment. This personal, individual climate, which we carry about with us, must not change if we are to continue to be effective. In order that the constancy of the internal environment may be assured, therefore, every considerable change in the outer world and every considerable move in relation to the outer world, must be attended by a rectifying process in the hidden world of the organism. The chief agency of this rectifying process, as we have just noted in many illustrations, is the sympathetic division of the autonomic nervous system.

Cannon further pointed out that animals deprived of the sympathetic nervous system can survive successfully within a protected environment provided by a quiet laboratory, but when such animals

¹³ Cannon, W. B. The Linacre Lecture on the Autonomic Nervous System, London, Cambridge University Press, 1930.

are forced to meet any struggle with temperature changes, muscular activity or emotion they promptly show failing function of all viscera equipped with smooth muscle

The gastric disturbance in cases of peptic ulcer in man, as well as the other signs of sympathetic nervous system weakness (e g, sweating, fatigue and wide palpebral fissures), forms a picture highly reminiscent of the sympathectomized animals. It would seem that these peptic ulcer people possess an inadequate sympathetic nervous system. This inadequacy may be the result either of an inherited weakness or of a wearing out process. The latter might well follow prolonged exposure to the chronic anxiety state just referred to. It is the nature of this anxiety that we propose to discuss later in the section dealing with the androgynous mosaic.

In order to demonstrate the subtle indications of the feminine component in the personality, the following psychologic histories are presented. Most of them are nonanalytic, and their objective nature makes it somewhat difficult to interpret them from an analytic point of view, yet their significance is quite apparent. We have made about sixty of these studies in all. From these, nine complete histories and fifteen excerpts have been selected for presentation.

It is not easy to gain access to the storehouse of a human being's emotional life, the intimate details of events that involve feelings and loyalties are jealously guarded. For this reason direct questions, or even leading ones, are invariably met at first with silence or negative response. Only when a friendly and dependable confidence has been established between patient and physician do the significant contents of the former's secret thought chamber appear. Much of this is unavailable to the too abrupt questioner, not because it is lost in the patient's subconscious mind, but because it is withheld for reasons of fear, loyalty or sensitiveness to tactlessness on the physician's part. When the proper relationship has been established, the concealed thoughts and later the subconscious residues will begin to distil over, hesitatingly at first and later sometimes with a gush that may in itself have a healing as well as a diagnostic value.

REPORT OF CASES

CASE 1—*Duodenal Ulcer*—This patient, T. D., was 34 years old and unmarried. He was of the classic ulcer type, with wide palpebral fissures, moist palms and chronic fatigue. An operation for duodenal ulcer was performed five years before consultation, and since then he had been under almost continual treatment for gastric distress. He came of New England stock, but his family moved to Texas shortly after his birth and he had lived there ever since. The circumstances of his birth were important. Shortly after he was conceived his father left home for no apparent reason and was not heard from again until the patient was 12 years old. During his early childhood, the boy frequently had the feeling that he was an

unwanted addition to the family. Furthermore, the mother was so occupied with her efforts to support the family that he saw little of her. He had two older brothers and two older sisters, one of whom had played the part of mother to him in his early years. Added to the feeling of insecurity which this parental lack produced was the quality of effeminacy which the boy himself recognized in his own personality. On this account, he became the butt of his playmates' ridicule. To compensate for, or to obliterate, these feminine traits, he consciously strove to develop masculine attitudes and behavior. He succeeded in this so well that people now often discuss the subject of effeminate men with him. "Of course they wouldn't do this," he went on, "if they suspected that I was like that." Furthermore, he had done well in business and by great determination had become the driving executive head of an important department of a large manufacturing business. He did not by nature possess ability or interest in executive work.

When he came to the Constitution Clinic, after five years of intermittent recurrences since his operation, he said that he was now convinced that his trouble was primarily nervous or mental. With great difficulty and resistance, although he had brought himself voluntarily to the task, he finally stated that he feared that he was homosexually inclined. Further inquiry, however, soon revealed that he had never had any actual sex experience with members of his own sex, and only very incomplete attempts with women. He remarked that his training in this phase of life had been one of stern puritanical repression, ignorance and fear. At the age of 10 he had become attached to the little daughter of the minister of the local Baptist church and subsequently became an ardent church-goer, largely, he thought, because it kept him in close association with the little girl. This attachment lasted until he was 17 or 18 years of age. At that time, he chanced to go to a service in a church of another denomination where he saw a young acolyte of great personal beauty. For the next few years he continued to be a most devoted attendant at the services in this church. He never met or spoke to the acolyte whom he held continually in his mind.

Six years previous to examination he fell in love with a woman who was self-supporting and earning an income considerably larger than his own. Their relationship advanced rapidly and intensely until sexual activities had almost reached the stage of intercourse. But at this point the patient was checked by the traditions of his ancestors and the teachings of his two churches. Marriage alone, by sanctification, could permit the final sexual act. On the other hand, if he married this woman whose earned income was quite adequate to support them both, though his was not, he would find himself in the humiliating position of a dependent on his wife. This was more than his already overtaxed masculine component could tolerate. In the face of this dilemma, he terminated the relationship abruptly. During the ensuing months, he sought a solution of this problem and finally attempted one by an effort which he said was purely rationalized and quite without an emotional conviction. He asked the woman to live with him, unmarried. This gesture was promptly and vigorously repudiated by the woman, and he retreated more than ever depressed over his defeat in life. Within a few months after this episode, his stomach symptoms began and grew increasingly worse until the operation was done.

During the course of work at the clinic, while the patient still believed himself to be homosexual, he had two interesting dreams in rapid succession. In the first, he ascended the stairs to his bedroom and, outside the door, he saw his two nephews, sitting at each end of a sofa, curled up in the attitude of fetuses. He walked past these without stopping, entered his room and closed the door. Within, he found his sister, who promptly changed into the girl he was somewhat interested in at

the time He made amorous advances toward her, which terminated in an emission The associations with this dream are significant The nephews, who appeared as infants, were actually full grown youths for whom he the patient had felt the possibility of homosexual attraction The sister was the one who had played the rôle of mother to him

In the second dream he entered a house with a push button entrance Three names were in the list beside the bells On the first floor was a count, on the second a prince and on the top the girl he was going to visit His eye ran up the list, past count and prince, and without hesitation he pressed the bell of the lady's apartment He started up the stairs and met many obstructions in the hall, composed of furniture Finally he reached the girl's room, entered and found her lying partially clad on the bed He again made amorous advances which concluded with an emission The association brought out the immediate linking of count and prince with homosexuality The obstructions were related to his traditions and the belief that he was unable to achieve a normal sexual life

Two days after these dreams the patient complained of a return of his gastric discomfort It was during the discussion of these symptoms and the preceding dreams that the patient brought out the account of the early attachment to the pastor's daughter, the acolyte and the love affair that was broken off before the original onset of the stomach symptoms On the basis of the foregoing history, the patient explained the return of his indigestion in the following way "It would seem that the phantasy love affairs with the parson's daughter and the acolyte were sanctified by my devotions in the two churches But the later love episode, in which marriage was impossible because of the blow to masculine pride, lacked the sanctification by the church and led to ulcer formation Now the recent dreams which display a phantasy sex fulfilment, unsanctified by marriage, have presented in phantasy (dream life) the same situation which existed in reality before the original ulcer"

Following the conference in which this piece of insight developed, the stomach symptoms receded and have not reappeared

Analysis of Family History—On the maternal side of the family, the women were replete with forcible qualities of personality The mother and two sisters of the mother were women of marked executive ability and were quite capable of assuming the rôle as heads of the family The maternal uncle was a chronic inebriate, lacked stability and definiteness of purpose, and showed little backbone in dealing with a domineering wife

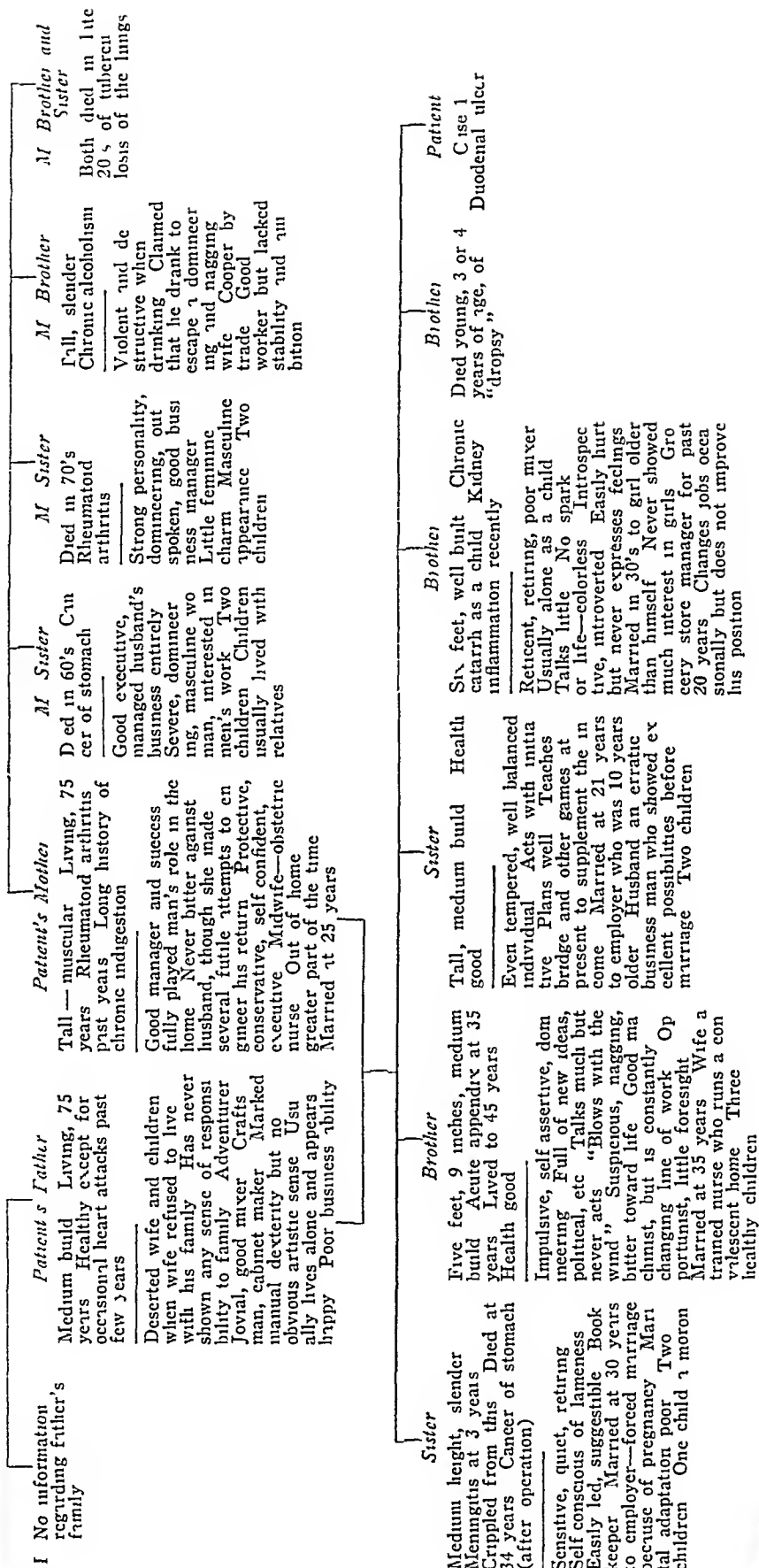
The patient's father was apparently more attached to his mother and sibs than to his own family and chose to desert his wife and children and reestablish himself in the household of his mother He had unusual manual dexterity but little business ability and courage

The absence of the influence of the father in the home seemed to express itself in the fact that both of the patient's sisters married their employers In neither case was the marital adjustment good Possibly, too, the absence of the father in the home helped in determining the patient's sense of insecurity Very early he felt the sting that he was an added burden to the family at a time when the father left the total responsibility to the mother The brothers showed the mother influence in their marriages The older one married a nurse, the mother was also a nurse His wife continued in her professional rôle He showed a marked feeling of insecurity and lack of stability in work The second brother married a woman older than himself and brought her to the family home in preference to establishing a home of his own

Schematic Pattern of Patient's Family History

CASE 1—Racial Extraction

Paternal, unknown, maternal, American, English extraction



The presence of a hereditary inferiority in the gastro-intestinal tract was also expressed. The mother gave a history of gastric disturbances. One of the mother's sisters and also the patient's oldest sister died of cancer of the stomach. Two cases of tuberculosis in the mother's family were also worthy of note.

All members of the family seemed to be of the long thin variety.

CASE 2—*Duodenal Ulcer* (P O ^{13a})—The patient, A. E., was 37 years of age. He was morphologically typical of the duodenal ulcer type. An operation for duodenal ulcer was done two and one-half years before consultation. There were constantly recurring symptoms of gastric disturbances.

The following is a brief sketch of the psychologic aspects of the case.

The patient was second in a fraternity of five children and was the only son. As will be seen from the schematic outline of the family history, the parental influence was of a negative character. The patient was highly emotional. He was inclined to be distractable in conversation and approached the point at issue in a circuitous manner. His experience memory was poor. He learned easily, but did not retain factual knowledge. He displayed a marked feeling of insecurity, and this expressed itself strongly in his vocational adjustment. As a research engineer he had had several marked successes. He stated, however, that his conclusions were reached largely by intuition, and that he could recount with difficulty the logical steps by which he must convince his co-workers. Consequently he preferred to work alone, because it gave him a greater sense of security. He offered his stomach trouble as the reason why he held a mediocre position. It enabled him to work under conditions which offered the least possible emotional and physical strain. The patient was meticulous in his dress and was finicky about food. The latter he said was so because of his indigestion, still he admitted that the discomfort continued despite the dietary precautions.

He was married at 33 years of age to a woman three years his senior. She had been his father's favorite music student and had so far identified herself with the family before she met the patient that she called him "father." The patient's only child, a daughter, was born eighteen months after marriage. She lived only two and one-half years, and died two months previous to the patient's first visit to the clinic. The marital relationship was greatly conditioned by the wife's religious views, but he insisted that total abstinence did not affect him adversely. "My stomach is bad and that takes a lot out of a fellow" (Or were his stomach symptoms a compensatory adjustment for this lack of virile expression?)

During the first few interviews the patient talked freely of himself, yet one gained the impression that there was something that greatly troubled him which he was unwilling to disclose. Finally one morning he told the following story.

At 18 years of age he had his first and only premarital experience with a woman. At this time he was infected with gonorrhea, but he did not report for treatment until the disease was far advanced. With proper therapy, however, all symptoms were relieved. Several years later he went to a competent physician, who, after repeated tests, was unable to find any gonococci. A subsequent examination, likewise negative, was made just previous to marriage. Yet in the patient's mind there always remained a doubt and a terrific feeling of guilt.

When he realized that his wife was to have a child, his fears increased and caused him to omit intercourse. During the period of pregnancy, his first gastric symptoms developed, and they grew increasingly worse as the pregnancy progressed. The final blow fell on him when the child was born a mongolian idiot.

13a In the case reports, P O indicates after operation, and N O, that an operation had not been performed.

To the patient this tragedy confirmed his secret fears, and he held himself directly responsible. The child's malformation became the constant evidence of his guilt. So great were his fear and humiliation that he never mentioned the infection to the physicians who took care of the child.

The patient was operated on for ulcer three months after the child's birth. While giving this point in the history, he asked "How could that operation help me when I had that child always before me?" He was unwilling to have another child. Consequently, because of her religious scruples, the wife refused intercourse. There still lurked in his mind the fear of infecting her, and he rationalized her resistance as only another penalty that he must pay for his guilt. At this interview the lack of any relationship between the condition of the child and his gonorrhea was carefully explained. The patient understood it and for the first time accepted it.

Ten days after the foregoing history was divulged the patient was anxious to review the effect of his confession. He said that the term "deliciously refreshed" most aptly described his new attitude toward life, and he reported that he and his wife had decided to have another child. The patient said that he thought this new and free relationship with his wife was also an important factor in changing his attitude, and in eliminating the sense of guilt that had previously inhibited his sexual life.

A week later the patient reported that he intended to move into a new apartment in order to get away from the constant reminders of the mongoloid child. His wife revived her interest in the further study of music. As a result of these changes, the patient found that he now could talk to his wife with the conviction of a man. There had been no gastric symptoms since the interview in which the gonorrhea episode was revealed, though the wife's studies necessitated his having the main meal away from home. This he had always carefully avoided in the past. Furthermore, he found that he had a different attitude toward his work, which was evidenced by the fact that boys in the office had been asking him lately what his good news was.

Further and more detailed analytic treatment with this patient does not seem necessary at the present time. He shows remarkably keen insight into his present condition and is intelligently making adjustments. Once the insufferable load of guilt was taken from his shoulders, his entire attitude toward life was altered.

Analysis of the Family History—The paternal grandfather was a chronic inebriate, and the responsibility for the care of the family was left to the grandmother, who displayed ability and domineering qualities of personality. This reverse in the home situation had probably conditioned the lives of the patient's father and his sibs. A sister and two brothers were never married. Of these three, two showed strong maternal attachments. The patient's father married at 18, adapted poorly, and at 50 gave up a brilliant musical career and returned to the childhood home and the business of the mother.

The patient's mother was unstable emotionally and at times was unable to cope with life's problems and retreated to drinking. Little is known of the members of her family.

The patient was an only son, and there were four daughters. Neither of the parents had a positive influence in the home, or in the life of this sensitive boy. None of the sisters had adapted well to marriage.

All the members of this family except the mother were of the long thin variety. The youngest sister of the patient showed the only other evidence of gastrointestinal weakness. Two cases of tuberculosis were found in the paternal line.

Schematic Pattern of Patient's Family History

CASE 2—Racial Extraction Irish

I	<u>F Father</u>		<u>F Mother</u>		<u>Pt's Father</u>		<u>Pt's Mother</u>		<u>Two Brothers, M Brother</u>		<u>M Sister</u>
	Died at 60 years Chronic alcoholism Owned small country store Unsuccessful wife managed business and family	Delirium Chronic alcoholism Owned small country store Unsuccessful wife managed business and family	Died at 80 years domineering woman, maintained the position as head of the family Managed business successfully		Living, 57 years Medium height, slender, sharp, finely chiseled features Health good	Living, 56 years Short, stout Delirium tremens in 30's Excessive drinking from 30-48 years		Died at 40-50 years of age No further information	Farmer in Michigan Not married		Quiet, retiring Married, several children No further information
II	<u>F Brother</u>	<u>F Brother</u>	<u>F Brother</u>	<u>F Sister</u>	<u>Pt's Father</u>		<u>Pt's Mother</u>		<u>Two Brothers, M Brother</u>		<u>M Sister</u>
	Lived to 60 years Athletic build Health good Wealthy successful merchant in Dub- lin Domineering personality Hobbies fishing and hunting Married Two children	Lived to 50's Athletic build Health good Accountant, moderately successful Fisher and hunter Never married Lives alone in regal bachelor style	Died in early 30's of tuberculosis of the hip Medium build Managed country store of mother Not married	Died in early 30's of tuberculosis Slender "Lived for and with mother" Fear of going out alone Few social contacts No men friends	Living, 57 years Medium height, slender, sharp, finely chiseled features Health good	Living, 56 years Short, stout Delirium tremens in 30's Excessive drinking from 30-48 years		Died at 40-50 years of age No further information	Farmer in Michigan Not married		Quiet, retiring Married, several children No further information
III	<u>Sister</u>	<u>Patient</u>	<u>Sister</u>	<u>Pt's Father</u>		<u>Pt's Mother</u>		<u>Two Brothers, M Brother</u>		<u>M Sister</u>	
	Medium height, slender Health good Took mother's place in the family Domineered at 20 years to physician Adaptation poor Extravagant, selfish Two children Little attention to or apparent interest in children	Medium height, slender Acute rheumatic fever at 15 years Duodenal ulcer See case 2	Medium height, slender Perfect—operative treatment Health good Quick tempered, erratic, in decisive Only member of family who defied father during his temper tantrums Came to America at 30 Married shortly afterward to ship acquaintance First male friendship, unhappy marriage—history of frequent separation with impending divorce Three children	Medium height, slender Club Health good Quick tempered, erratic, in decisive Only member of family who defied father during his temper tantrums Came to America at 30 Married shortly afterward to ship acquaintance First male friendship, unhappy marriage—history of frequent separation with impending divorce Three children	Short, slender of chronic eczema during childhood	Long history Quiet, gentle, sensitive Usually cried during family quarrels Married at 23 to a physician Three children Constant friction Money distribution and his attention to other women Divorced She now manages a hotel and is a successful executive		Medium height, slender Chronic constipation Indigestion—crue in selection of food controls this Living, 23 years			

CASE 3—*Gastric Ulcer (P O)*—In order to save space, the routine hospital history of the gastric disturbance will be omitted. The patient, R L, had a classic case of peptic ulcer of the lesser curvature and received both medical and surgical treatment. Not only did his stomach symptoms recur, but other evidences of vegetative nervous system maladjustment developed, for example, sweating, trembling and fatigue. The following notes are presented in order to display something of the patient's "man-environment unit."

Morphologically, the patient showed that in thirty characters and indexes, 73 per cent fell well within the values that have been established for the ulcer group. It is interesting to note that the gonial angle, which has been found to be one of the most constantly specific characters in different constitutional types, in this instance was 106 degrees, a figure far more typical of the gallbladder race than of the ulcer race.

On April 26, 1926, a partial gastrectomy with entero-enterostomy and gastro-jejunosomy was performed. The patient made a good recovery and was discharged on March 30.

On March 3, 1927, the patient was in good condition as far as the gastrointestinal tract was concerned. He was a bit underweight. He belched gas slightly.

On March 8, 1928, he continued in good shape, and was working regularly.

On October 19, there was no recurrence of the gastric symptoms, but the patient was troubled with profuse sweating. He presented another example of anxiety as a factor in the production of ulcer.

At this point the patient was turned over to the Constitution Clinic.

On Oct 31, 1928, the patient presented a remarkable instance of the effects of chronic fear. His emotional maladjustment began at an early age with the experience of watching his terrific mother knocking out his drunken father and seeing the latter crawl ignominiously off to bed. But his mother never hit him, and he always felt happy and secure in her presence. After her death he was practically thrown out of his home by an older sister who took charge. A year or so later, at 16, he married, and he became a father at 18. After the third child he could not meet expenses and suffered the humiliation of breaking up his new home and seeing his wife go back to her mother. Subsequently he got it established again. Then came a revival of father troubles, ending in the forcible eviction of the drunken man from his house. Later his wife metaphorically beat him (the patient) over differences of opinion. After one of these altercations, he crawled off to bed with a sense of defeat, saying "I never win." Yet in nightmares he was in dire difficulties and always waked calling his wife for help. Eleven years before examination he ran over and killed a child with his motor truck. He was acquitted, however, for years he was irritable at home. Further trouble developed with his father, and he was irritated at having the court order him to contribute to this parent's support. A conflict appeared. If he gave up driving the truck, he faced the loss of his home. But driving a truck revived the fears associated with the killing of the child. The patient then began to get insight. As a result, the sweats stopped, sleep became sound and normal, appetite returned, weight increased $2\frac{1}{4}$ pounds (1 Kg) in ten days, and altogether he felt like a new man.

On November 7, the patient said that he had been eating better lunches without symptoms. He had no more sweats. He was less irritable with children. He noticed that he worried less. He was trying the device of asking his children for advice in small matters, and it worked well. He complained of headaches. The top of the head was flushed.

On December 12, the patient continued to do well. There was an interesting relapse of sweating following a motor accident on a hillside the week before. The patient saw its import and felt very well the week of examination. He had gained a little more weight.

On Jan 11, 1929, the patient had gained 2 pounds more (0.9 Kg)—he now weighed 137 pounds (62.1 Kg)—a total gain of 5½ pounds (2.5 Kg) since Oct 31, 1928. He had had no more sweats. He felt fine, he did not have gastric symptoms and he ate practically everything.

On March 21, 1929, the patient had no complaints, he was free from sweats, his nervousness was limited to driving a truck in very slippery weather. He weighed 139 pounds (63 Kg).

On April 19, the patient showed a marked improvement since starting work in the Constitution Clinic on Oct 19, 1928. He had indulged, however, in food that seemed to be putting unnecessary stress on his stomach. Occasionally, he ate corned beef and cabbage and other indigestible foods. He was advised to follow a bland nourishing diet without restrictions except such vegetables and fruits as were apt to be tasted after eating or repeating vegetables. The patient was advised to return to the Constitution Clinic.

On Oct 18, 1929, the patient had no pain or distress after meals. He was not on any diet. He was driving a truck as usual without dread.

On November 15, he said that five days previously, following a choking spell on drinking water, he vomited a teacupful of bright red blood. This stopped spontaneously, and he had had no recurrence.

The patient had a friend—an assistant timekeeper in the same firm in which he worked—with whom he used to compare symptoms. The friend's symptoms were attributed to gas in the stomach pressing on the heart. On Monday, November 4, the patient heard that this friend had died two days before while reaching for the paper at home. From October 21 to 29, the patient had been off work because of a cold. Worry over the friend and his own past symptoms made work more nerve-racking for the patient, and thus led to fear of consequences of leaving the job again.

Hemorrhage occurred on Sunday morning, November 10. (This six day interval is characteristic of what we have found—usually a hemorrhage seems to occur from two to six days after the inciting cause.)

The patient talked to me for nearly two hours. He said that all the trouble started two years after his father came to stay with him in 1923. (Fifteen years previously his father lived with a married daughter, she promptly got stomach symptoms and paid \$50 a week to doctors as long as the father lived with her. When he left, all her symptoms disappeared.) The patient unconsciously used interesting expressions in speaking of his father. "He used to turn my stomach", then, referring to the money (\$2.50 a week) he contributed to his father's support, he said, "Why should I bleed myself to death for him after the deal he gave me as a child?"

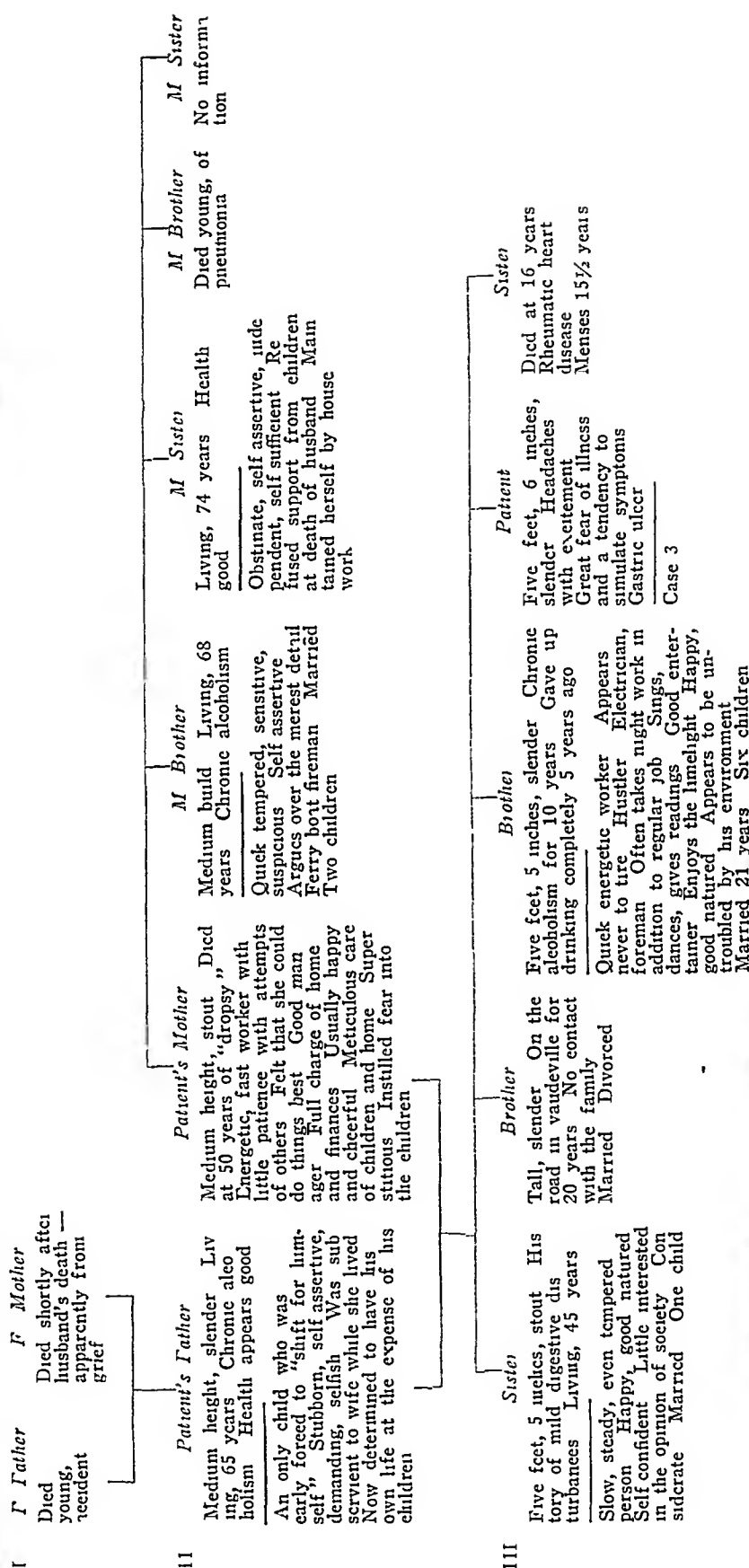
The patient's dreams of death may have come from the repeated remarks made by the father. "Don't talk to me about drinking—you'll be dead before me."

On Oct 10, 1930, there were no symptoms referable to the patient's digestion, except occasional belching of gas when he ate too big a meal. He had recently had a fractured left arm which had laid him up and prevented him from working.

Summary—The father's alcoholism and the accident of killing the child with a truck were, of course, serious blows. However, in view of the fact that the patient had seen the power of his mother over his father and his own experience with his wife's power over him, his failure to hold his home together was even

Schematic Pattern of Patient's Family History

CASE 3—*Racial Extraction* Irish *Both parents born in Southern Ireland*



more destructive. He had attempted at a very early age to demonstrate that he was a man, but he had failed to achieve the standards of manliness which he had set for himself. Furthermore, he was very precise and fussy over details about the house. In telling every one his faults, he displayed a masochistic tendency. He thought that people tried to humiliate him by showing that they were more capable of financial success than he was.

Analysis of Family History—The patient's father was alcoholic and domineering, and he continued to be a destructive influence in the patient's life. The mother and her sisters showed definite virile trends. The mother was a combination of calmness and good nature and an urge to manage and carry on alone without cooperation. A maternal uncle evidently had an ulcer psyche pattern.

Two of the patient's brothers showed artistic leanings and were driving, restless spirits. The living sister was the opposite, a quiet, calm housewife with marked maternal interests. The youngest sister of the patient had rheumatic heart disease and died at 16 years of age with the onset of the menses.

In general, this family represents the tall, thin type, though the mother and sister are short and thick set. Several instances of evident gastro-intestinal weakness appear.

CASE 4—Duodenal Ulcer (NO)—The patient, F. L., was a woman of 35 years who looked about 25. She was of a tall, slender build, and except for the gonial angle of 118 degrees was a classic example of the ulcer race. At 78 her father was a healthy man, though at 40 he had a nervous breakdown. Her mother was 78 and a very vigorous dominating person. The patient had two sisters, one older and one younger than herself. The oldest was injured in childhood and had been mentally and physically retarded ever since. The patient grew at the average rate, but her menstruation did not begin until she was 18 years and 10 months old. Up to that time she had been involved in what she described at first as a childhood and then a platonic boy and girl friendship, apparently utterly unaware of the significance of a possible love emotion. When she one day suddenly realized that the nature of the relationship had changed, she began to feel ill, and a few days later she had her first gastric hemorrhage. She was 19 years old at the time, and soon afterward she became engaged to this friend and marriage was much talked of for two and a half years. The engagement was broken, however, by the fiancé, who felt that he could not face the responsibility of a sick wife. The patient herself recognized that the prolonged gastric invalidism, which required great care and treatment for the whole of the following year, was a protection against further advance into a love relationship and marriage. Yet when her sister informed her that her former fiancé was again engaged to be married, she became most indignant. When she was 23 years old, she had an attack of mumps with ovarian involvement. The patient became engaged again when she was 25, but there was great vacillation about the marriage, which was arranged for and postponed many times. During this period she became involved with another man, and had an incomplete intercourse which resulted in pregnancy. This was interrupted at the second month, and for the following year the patient was in a very poor state of general health with much gastric disturbance. Subsequently she resumed sex relations with her fiancé, although never satisfactorily, and this state of affairs went on for the next two or three years. The question of marriage was continually discussed and postponed.

Two years before examination her fiancé told her that he had ceased to love her and had given up the plan of spending the summer with her. Twenty-four hours after he delivered this ultimatum, she had a severe gastric hemorrhage. Her recovery from this attack was slow. She presented herself at the clinic with the

history that she was constantly fatigued, could eat almost nothing without subsequent distress and was often moved to tears at the slightest emotion. About three months before admission she had received a cable from her fiancé saying that he was not coming to Europe as planned to join her. Within twelve hours, she suffered from a return of gastric distress with vomiting.

As the patient told her story, she made continual references to her need of some dependable human relationship. "I must have one person whom I can trust completely." Yet she perceived that all the men she had turned to had been quite vacillating and undependable. "Indeed," she declared, "every man I've been in love with has developed some reason why at the last moment the relationship had to be broken." She found them all "unlike my wonderful father who is the only man I've ever known who embodies all the virtues, and particularly the great essential quality of loyalty."

The suggestion was then made to her that perhaps her own attitude toward the opposite sex had an antagonistic element in it which led her to select men essentially unsuitable for permanent mates, or that perhaps she had an unconscious resistance to marriage itself. Such possibilities were consciously denied, but within a few days she dreamed that she attended an entertainment. At the door a boy said to her "come in here and see the show we men are going to give." The immediate association took her back to events that had occurred when she was 5, which she had not thought of for many years. At that time she had been living with her aunt because of her father's illness, and she recalled the terror she had experienced every day on going out into the garden. There she was tormented and frightened by a small boy who chased her and pulled her hair. For several interviews these apparently harmless gestures were recounted as the only ones. But finally, with tears and averted gaze, displaying emotional disturbance and embarrassment out of all proportion, she stated that the little boy had likewise made her acutely ill with nausea and vomiting by the exposure of his genital organs.

The patient soon began to realize that all her emotional reactions were of an extremely childish sort. She confessed to a strong desire to consort with her younger sister's friends, and she noted herself the swift change from tears to laughter which so characterized her. She had gained insight into the mechanism of her retarded psychosexual development represented by her late menstrual onset, the avoidance of marriage, the incomplete sexual relations and the idealization of the father. On the thinking or rational side, she had attempted a compensatory effort at independence and self-sufficiency. With the growth of insight, there had been a definite gain in vigor and the ability to eat any kind of food without distress.

Analysis of Family History—Longevity appeared in the maternal line. The mother and all of her sisters seemed to be of a vigorous and striking personality with tremendous driving force. There was a distinctly low interest in marriage associated with strong church affiliations. The mother of the patient exhibited a marked inferiority complex with a nervous drive to overcome this. One brother had been married three times.

There was a strong trend of nervous instability in the father characterized by complete collapse in the face of difficulties. He displayed terrific driving force in his work.

Neither the patient nor her two sisters were married. The oldest suffered from a mental breakdown following a spinal injury at 19 years. At 38 years she showed rather good recovery through suggestive treatment. The youngest sister was 28 years of age. She was a rather timid, retiring, introspective girl, with a sense of insecurity covered by an attitude of blasé boredom.

Old American, English extraction

CASE 4—Racial Extraction

	<i>M Father</i>		<i>Mother</i>		<i>M Sister</i>		<i>M Sister</i>		<i>M Sister</i>		<i>M Sister</i>		<i>M Brother</i>		<i>M Brother</i>		<i>All</i>			
	Tall, well built, vigorous man at 86 years Premature gray hair		Died at 86 years Premature gray hair		Mechanic—successful Active in business until 80 years of age		No information members of her family died in the same accident		All											
I	<i>Father</i> Five feet, 10 inches, thin, wiry 75 years Health good Tender, sympathetic, tolerant Highly suggestible Abnormal fear of death Man of terrific energy and nervous activity Several periods of depressive psychosis 40-50 years of age Always subject to marked depressions due to a sympathetic response to another's troubles Successful engineer Married at 35 years		<i>Mother</i> Five feet, 5 inches, 165 pounds Living, 78 years "Remarkable physique" Premature gray hair Self conscious, timid, nervous, easily excitable Social functions followed by complete physical exhaustion Constantly nagging over details in the family, genial and courteous to strangers Dependable in emergencies, collapses when strain is past Married at 37 years		<i>M Sister</i> Five feet, 6 inches, slender Living, 86 years Active, healthy Premature gray hair Severe Puritanical type Irritable, fussy Worries herself and all around her regarding details Enthusiastic church worker At present does all of her shopping and never seems to tire Not married		<i>M Sister</i> Medium height, slender Living, 83 years Health excellent Premature gray hair Much like spinster sister in temperament They live together and share the same interests Married young, husband died shortly after marriage No further interest in marriage.		<i>M Sister</i> Died young, childbirth No further information Dictatorial, domineering "Rules the roost," Unbending Puritan No children		<i>M Sister</i> Short, medium Living, 60 years Health good Successful merchant in father's business Married No children		<i>M Brother</i> Six feet, 2 inches, well built Living, 62 years Health good Successful		<i>M Brother</i> Five feet, 9 inches, medium Living, 52 years Health good Premature gray hair Actively identified with liberal politics since 30 years of age Independent in action Broke from Puritan traditions of the family Genial, well liked, carefree person Nervous habit of twitching hand Otherwise, always calm and well poised Married three times Wives were all active forceful women					
II	<i>Sister</i> Five feet, 7 inches, medium build Accident to spine at 19 years Slow physical recovery followed by mental disturbances at present Living, 38 years Introspective, silent, deep interest in religion Self conscious, hesitant in speech Powers of observation keen Tense nervous contraction of muscles Whole personality probably conditioned by after effects of accident		<i>Patient</i> Five feet, 7 inches, 120 pounds Living, 35 years Duodenal ulcer See case 4		<i>Miscarriages</i> Two or three in succession One known to be a male		<i>Sister</i> Five feet, 7 inches, 120 pounds Health good Outwardly complacent, calm, undisturbed by environment, self sufficient "Lives within herself, no one ever knows what she is thinking or planning" Really somewhat timidly retiring and socially insecure Closest friends are women Little interest in marriage													

Self-Estimate The patient did not usually feel ill at ease or timid, though as a child he was. He was rather negatively suggestible, stubborn and conceited. He sought company, though he did not become lonesome easily. He was confident of himself as a driver. He was very frank and open. He liked to be the center of attraction, and was rather vain. He was generous to a fault. He was not guided by principle, but grasped opportunities. He drove very well in traffic. He changed jobs frequently. He was always "looking for a stroke of luck." He accepted new plans quickly.

Mood and Emotional Reaction The patient was usually cheerful and optimistic. His mood was variable. He said that he was "quick on the trigger," but was over his temper quickly. Painful stimuli gave a marked reaction. He was neurotic and complained under pain and discomfort. He was rather easy to frighten. He cited instances in which fright caused "dripping perspiration." He said that as a child he was "cowed" by his fellows. He was easily elated by pleasure. He did not worry or harbor grudges long, he forgave easily. He said "Kind words take the fight out of me."

Adaptation Imperative The patient was not really ambitious, he was not very courageous, and he had little real initiative. He was somewhat vigorous minded. He said "Opposition stirs me on." He had liked active sports as a boy. Carpentry was his hobby. He liked the theater. He enjoyed a few games. He was still interested in penmanship and wrote a very pretty hand. He read books on psychology and was interested in "self-analysis." He said that he "tries to find out hidden meanings." He used little restraint in the appetites, fears or passions displayed.

Evidently this patient is fussy over details of food and dress, is vain and fond of attention and has not been successful in his two marriages. He was shy in childhood, easily frightened and cowed by his fellows. His statement that "kind words take the fight out of me" bespeaks of an emotional sentimentalism, not of distinctly masculine character. Yet it should be noted that his heterosexual urge and activity are unusually strong.

CASE 6 (65118) —Duodenal Ulcer (P O) —Family History—Paternal The father was of English stock (Bermuda). The father's father was a ship builder. He was a "neurotic in the end." The father died of stomach trouble at 65 years of age. He was a tradesman and cooper. He was of medium size, thin and nervous. He was a great smoker. He married a second time when the patient, N B, was 25. One of the father's brothers was slightly weak-minded "due to drink," and died at 40 years of alcoholism. Another of the father's brothers died of smallpox (no age given). Still another brother died at 68 years of stone in the kidney.

Maternal The mother was of Scotch stock. The mother's father was a sea captain, he taught navigation in Bermuda. She was a fine type. The mother's mother died of heart disease at 64 years. She was rather small, very thin and active, she was always in a hurry, ran and never walked. She usually seemed tired.

Siblings There were five sisters, two were dead. One "went off her head" and tried to commit suicide. Spinal difficulty and "efforts of a doctor to cure this, resulted in loss of mind." The oldest sister was 74 years of age. One brother was 72 years of age and worked regularly as a stone mason. He had seven children.

by his first wife and four by his second. Another brother was alive and well at 57 years. One sister was a neurotic, she had dysfunction of the liver.

Personal History—The patient had a fairly happy childhood. He had to do many chores, yet, he had time for things of other sorts. His father was a good companion. The patient was not considered a healthy child, he had many colds, mumps, chickenpox, measles and scarlet fever. He was ill during the latter part of his life. He had scarlet fever when he was 40 years old. An operation had been performed on the kidneys some years before examination, either for infection or for stone.

The patient went to school at 10 years of age and did fairly well. However, he left school at 14 years so as to be made "useful." He was sent to learn the trade of harness making. His father always directed his course and never allowed him to do what he wanted, invariably he was told what to do.

The symptoms of the present illness dated back a long time. The first serious symptoms appeared in 1912, when the patient was a steward of a country club in Flushing, N. Y. His position was congenial, but there was a good deal of drunkenness among the members. He had to handle them with care, this was a strain, also, there was night work with irregular hours. However, the patient could think of no sharply precipitating cause of the present condition.

Personality—Intellectual Activities. The patient learned easily. He was good in spelling, he liked geography. He was not good in mathematics. He had always tried to please in his positions, but he had a roving disposition and liked to change.

His retention for recent events was rather poor, he remembered remote experiences more easily than recent experiences. His visual memory was good. His power of concentration had always been bad, chiefly because he "sees too many things at once." The patient said that he was overtimid and lacked initiative, he was not bold enough. He spent money very unwisely, if it had not been for his wife, he would not have had any.

He was very good with his hands, but not dextrous.

The patient had handled small groups of men (thirty) successfully. He has a good respect for the rights of others. He was imaginative.

His dreams were generally very horrible. One night he dreamed he had poisoned his father. His head was separate from the body. He placed it on the table and asked it to forgive him. There was no answer, but the eyes opened and shut. He awoke in horror. On going to sleep again, the head was still there, it asked him to stoop down. The patient then felt the cold lips on his ear. He awoke in horror. This dream stayed with him for weeks. Again he dreamed that he had crawled through a tunnel in a sand pit, and was almost suffocated. Also many black cats scratched him. He felt blood from the scratches. A friend, an older man, said that he would help him out, then another black cat scratched him. The dreams were always frightening and distressing. Since he had been in the hospital, the dreams had always been of bodily discomfort. He did not walk in his sleep.

The patient was truthful. He was not introspective. He liked nature and studied people. He left himself out of the picture, because he did not want to become nervous.

Before operation on the kidney he was very sorry for himself.

Somatic Demands. The patient did not use alcohol or tobacco. He had had the habit of biting his nails in childhood.

He liked attention, but did not seek it. He knew his capabilities and his limitations. He had a horror of the sight of blood. Once he saw a veterinarian open a horse, and this made him sick (10 years old).

As a child he was much frightened after dark, on coming up the cellar stairs, he ran lest someone catch his leg. He was very timid when learning to swim, he always imagined that a fish would bite him. He demanded activity. He tired easily and would often go home after playing games involving physical exertion, complaining of pain in his side, he was made to sit in a chair. He was not pugnacious, and was easily cowed by older boys. At school an older boy rather protected him. He was a continual worker.

In his sex-life, the patient was prudish and bashful. He practiced the average amount of masturbation. He had many girl companions. His sex experience was not excessive. His urge was naturally heterosexual. He avoided all suggestion of homosexuality. The patient had feminist trends. He sought friends among those from whom he could learn, his men friends were older.

The patient was especially (emphatic) attached to his mother. He married at 37. His mother died when he was 21 or 22 years old. He had been married twenty-one years and had no children. His wife was living.

He had a strong attachment to his brother and sister, they corresponded. He was always homesick until he married. His marriage was very successful.

Self-Estimate The patient was not bashful or ill at ease in a crowd. A lack of schooling or training had held him back. He felt sort of "half-finished." He said "Being a butler is not much to be proud of."

He was very trusting. He said "I distrust no one till I find him out, and then that's the last of him."

He was handicapped with nerves. If there was a heated argument, he moved away. He said "I wouldn't make a soldier." If he saw a brawl he turned away. He liked everything to go smoothly. The last few years he had struggled to accumulate enough to leave his wife comfortably off. This attempt had not been successful and had made him anxious. He was very loyal. While his feelings were easily wounded, he did not become angry or irritable. An injustice rankled within him. Anger always expended itself in his epigastric region (he pointed to it).

The patient was overreticent and very precise. His wife shook him out of this. He was tactful and not suspicious. People treated him well, he said, but he had few friends.

Mood and Emotional Reactions The patient was generally cheerful, he was stable. He became unhappy quickly at times. He reacted buoyantly to pleasurable stimuli. His reaction to painful stimuli was slow, but it lasted long. The loss of a friend through death was hard. His fear of criticism was a tender point, he wanted to be well thought of. Physical fear was not a factor. Once, when the patient was almost run over by a motor, his only reaction was "how lucky it was on the right side and not on the left" (he had had a kidney operation on the left). He did not think that he reacted markedly to fear. He was inclined to brood.

Adaptation Imperative The patient formerly had had ambitions to become an artist, a fine handworker or a jeweler, but his father forced him without discussion into the harness making trade. He left this work and took up tailoring for five years, he became a fairly good tailor. Then he went on a ship as steward and developed a roving disposition. Then he did club work and worked as a butler.

The patient thought that he was overcautious, he did not like to risk what he had. Initiative appeared only if in connection with something he knew about (caution again?). The patient was by all means a follower. His chief satisfaction was derived from his wife and home. He was not interested in sports. He liked reading and traveling. He was fond of music, especially sacred (there was much feminism in his intonations, expressions, etc.) He had always been a church

member, and was fairly religious. He attended church when at home. He did not enter into politics, he could not stand heated discussions. He showed a conscious restraint of anger, fear and appetites. He said that it was "No job to control at all."

Special Traits The patient thought that he could have been a painter or an artist. He occasionally did some painting in water-color, usually of flowers.

This patient was quite noticeably feministic in his general bearing. He frankly admits that he would not make a soldier. His mother attachment is indicated both by his murder dreams and by the fifteen year delay in marriage after her death. His feminism is suggested also by his occupation as butler. He should have been an artist but for his father, who overrode his ambitions.

The following excerpts from other histories also in some instances indicate the tendency to overexpress a masculine attitude. The emphasis is so great that one is led to suspect that the opposite influence is very strongly developed in the unconscious. In other cases, the histories display the patient's difficulty or inability to play a vigorous masculine rôle in life.

Gastric Ulcer Males—The following cases are typical examples of the types mentioned.

CASE 7—For two years the patient was a cook. Later he took up the trade of bricklaying. He said of his driving activity "I am the fastest bricklayer in New York." He boasted that as a boy he always won a fight. He felt that a refusal to accept help from his wife in any situation typified his independence of action. He said "I have more self-control than any ten ordinary men," and yet the next sentence was "I never let a habit get the best of me for once they are formed they get the upper hand." He boasted that no man could misuse him.

CASE 8—The patient had the habit of nail-biting up to 14 years of age. He was a letter carrier. He was active in the time of danger, but crumpled up when the emergency passed. He said "I ate up my feelings when serving at the front and didn't digest them." His father had chronic alcoholism. The patient felt that his early home life was largely responsible for his emotional disturbances. His child's illness precipitated his ulcer attack. He was overly protective of his wife, and during this time he ate every meal for fear that she might suspect the gravity of the situation. (Here he found himself unable to play a wholly protective masculine rôle.)

CASE 10—The patient was the youngest of nine children. He boasted of his love affairs, but at 33 he was still looking for the "right red-headed girl." He said "I could go to a dance every night in the week—yet I like to play cards and stay around with the fellows." He drank excessively.

CASE 11—The patient was a tailor. He had tried other occupations, such as chauffeur and automobile mechanic, but he always came back to tailoring. He married at 21 years. He showed extreme resentment of his stepmother and half-sibs. He particularly enjoyed describing the raw deal life had given him, and his disposition was of the feminine masochistic type. He was indecisive.

CASE 12—The patient had been self-supporting since 14 years of age. He left trade school to get a job. He planned his work well and was fairly successful as a contract painter. He married at 23 years. He said "I was never able to leave

the ladies alone" Yet he was a regular joiner and was a member of thirteen men's lodges He was an anxious, suspicious individual He had materialistic standards He said "Have as much money as the other fellow and he won't look down on you" He was timid and bashful, and he said "People try to make me look little" He traveled for prestige, he said "It puts me above the other fellow" (He was evidently very unsure of his masculinity)

Duodenal Ulcer Males—The following cases are typical of the types mentioned

CASE 13—A layman friend of this patient wrote a letter about him from which the following excerpt is taken

"In my house J was unstable, not responsible always, the same mixture of dreamer and drifter and keen pursuer of favorite ideas His personal character was somewhat of the same mixture He was unfailingly kind to the women in our group, even gentle in a sense usually understood as the characteristic of women rather than men His sympathy would extend to the point of his own personal suffering He was inarticulate usually, and upon his own difficulties very nearly silent It was especially hard to watch his health because he resisted any attempt to do so and went around sometimes in silent agony because he could not bear to let anyone know he was so unmanly as to be sick"

CASE 14—This patient's symptoms began with the onset of the wife's first pregnancy They increased throughout, and shortly after delivery, the ulcer perforated He made a good recovery Four years later, when the wife started her second pregnancy, he again began to have gastric symptoms He stated that it upset him terribly to be responsible for his wife's discomfort, it made him nervous and caused him to feel like a brute Indeed, he had the obsession of being almost the criminal cause of her condition and feared that she might die in childbirth This patient was a classic type, small, slender and high-strung His palpebral fissures were very wide, and he was always driving at his work He managed the whole office, went out after new work and generally did the work of ten men

CASE 15—This patient said "I am not afraid of anything, why I'd dive into deep water before I could swim" He boasted of his heterosexual urge, "simply can't leave the women alone" Yet he married at 33 a woman older than himself, and he admitted on careful questioning that he was actually very timid with women He was an old maid in respect to orderliness, he would leave the table to put something in place, otherwise, he would not digest his food He said "Painted face, dirty neck, well dressed men with shoes run down at the heel annoy me most" He was of the subservient servant type, he was a chauffeur and an apartment house superintendent He changed his job often He said that he "never had a row with the boss"

CASE 16—The patient was married at 20 years He said "I can do in one day what it will take another man two days to do" He was extremely sentimental and demonstrative He fainted when frightened He was weak and trembling when he had to confront his superior in his work He was a Fifth Avenue bus conductor, and was markedly solicitous of the safety and comfort of his passengers

In all of these histories and excerpts there is to be found a subtle and convincing evidence of the strong desire to overexpress virility The same principles can be seen through the personalities of the female

patients The following three complete studies of female patients are given as examples

CASE 17 (36753) —*Duodenal Ulcer (P O)*

Family History—*Paternal* The father was of English stock The history of the father's father and mother was not known The father died at 56 of "lung trouble," he also had dysentery

Maternal The history of the mother's father and mother was not known The mother died of tuberculosis of the lungs

Siblings One brother died during the Civil War Another brother died of tuberculosis, and still another brother died of "heart trouble" A sister died of tuberculosis of the lungs

Personal History—The patient, M T, was very ill and was slow in her answers, but she seemed quite clear in the information she gave She was born on a farm in the middle west, where she remembered a happy childhood She was a tomboy Her menstrual history started at 13 She was educated in private schools, and she traveled abroad several times She started to write when a young girl, and she wrote words for Moody and Sankey hymns The patient said that she had had "stomach trouble" since childhood She married at 30 She never wanted children and caused abortions every time she was pregnant

Personality—*Intellectual Activities* The patient learned easily in school, except in regard to mathematics She disliked to study and was very distractible, almost flighty Her power of concentration was excellent for short periods, but not for any length of time Her memory was good in the visual field, but poor in the auditory field Her experience memory was easily the best On a previous admission, it was noted in the charts that she had a particularly bad memory for numbers and dates She planned poorly, she said "it is too much bother" She had shown rather bad judgment all her life

The patient was very clumsy with her hands, she disliked housework or anything manual She was a good executive She had been a dilettante at many things writing, politics, women's rights, etc She was not able to save money, but she said she had "stingy streaks," and was never without something

The patient would not be called dreamy or visionary She was very truthful and careful of the rights of others She was definitely extroverted

Somatic Demands The patient was not particularly fond of her own comfort, she was not vain and was not very anxious for the affection of others She had been a very hearty eater She drank six or seven cups of coffee a day She was always in a hurry, she worked hard all the while She said that she "has crazes for things" She would be called pushing and aggressive She was adapted poorly to marriage She was a "tomboy" in her youth and early womanhood She married at 30, sex relations were not pleasant She had no desire for children and always induced abortions She seemed to be a very well adjusted homosexual She spoke of her husband as a "wonderful, simple little man" She said "I have a good deal of masculinity"

Self-Estimate The patient would seem to be quite self-confident and showed a feeling of insecurity only indirectly She was rather negatively suggestible and stubborn She was poor company for herself, and liked companions She was frank and open in her attitude toward those whose opinions she respected She was not vain, but "adored success" During a previous admission, she was delirious and expressed definite delusions, indirectly, perhaps, a fundamental suspiciousness (which might link up with homosexuality?) She was generous and not bound by principle, and she behaved definitely as an opportunist

Adaptation Imperative The patient was usually cheerful and optimistic, but said that she had rather marked and quickly succeeding swings of mood. She was quickly excited. She did not remember having ever been frightened, but she said that she would not have children because she was "afraid of the pain." She was not easily elated. Her moods were transient.

When the patient was ill or had pain, she became quite weak, though she claimed not to be affected. She said "I hate to see women suffer."

She was ambitious and vigorous minded. She had a large number of outside recreative activities, but none was very engrossing. She always liked politics, and had gone to church occasionally. Lately she had become interested in Christian Science.

The patient had little tendency to repress her appetites or temper. She believed that she was brave, but really she was not. She said that she "has a hard time handling herself."

Again the "tomboy" appears. The patient disliked housework and the usual manual work of women but enjoyed directing things. She said "I have a good deal of masculinity in me." Her adjustments were not good, and there is some reason to believe that there was a strong homosexual trend.

CASE 18 (640066) —*Duodenal Ulcer (Confirmed by the X-Rays)*

Family History—**Paternal** The father's father and mother were German. The father had died at 72 of pneumonia. He had "acute bronchitis," lumbago at 21, and "stomach trouble all his life." He was tall and thin and had angular features (he resembled the patient, J. P.). He was cranky, a scold, and fussy about food. He was not affectionate toward his children. He was artistic, and was very bitter against religion. He "thought churches materialistic."

Maternal The mother's father and mother were German. The mother was also German. She died at 52, of cardiorenal disease (asthma and kidney trouble). She was short and plump. She was easy going, but was worrisome by spells. She was religious. She got along well with others. The mother's sister died at 70. She never married, she resembled the mother (she was short and plump). She was a governess.

Siblings A brother died of "spinal meningitis" at 29. The trouble started with an earache; he was sick for one week. He resembled the mother in morphology and psychology. The history of the second child was not known. The third child, a sister, died at 15 months, of scarlet fever. Another sister had recently developed double vision and aches and pains. She was tall and wiry. She weighed 95 pounds (43.1 Kg.). The fifth child, a brother, died of "summer complaint." A sister died of acute appendicitis at 26. She was tall and angular, and resembled the patient.

Patient's Son The son had had appendicitis. He was tall and angular. He was easy going, he was not married, and was quiet and agreeable.

Personal History—The details of the patient's birth were not known. The history of her infancy was not known, except for scarlet fever. Her childhood was unhappy. The father was grouchy and not affectionate. The cervical lymph nodes had been enlarged and suppurating at 6 to 8 years of age, and required an operation, which left scars. The patient was sensitive about the deformity.

She was afraid of dark rooms and afraid to be alone. She would not undress until she had looked under the bed.

The patient liked active games and played with boys, but she did not believe that she was considered a tomboy

She married at 19 Her married life was not particularly happy A sexual adjustment was rather difficult The patient said that her husband was "sporty," a gambler, and was unfaithful to her He died when the patient was 27 years old

The patient had tuberculosis of the lungs when she was 31 years old She spent one year at Saranac and recovered She was able to support herself and her son by her own efforts till the son obtained a position He then supported her

Personality—Intellectual Activities The patient was probably somewhat slow to learn She left school at 16, when she was in the eighth grade (she was kept back somewhat by the tuberculous nodes?) Arithmetic and grammar were done poorly, history, geography and spelling were liked

The patient believed that she was always rather distractible She said that she "has many things going at the same time" She concentrated well for a short time She was not very introspective and did not look into her own personal problems clearly

Her memory was fair, it was better in the auditory than in the visual field The patient had little sense of location and forgot her childhood German almost completely She did not recognize faces very well Her common sense judgment was fair, except in regard to money, she had not saved She planned housework well, but not other things She was rather quick in making decisions She was fairly successful as an executive in a small way

The patient was not considered visionary or dreamy, and she was not introspective Her night dreams were unpleasant, they were of falling, sinking or being chased She was truthful, but was not particularly careful in regard to the rights of others

Somatic Demands The patient's appetite was usually good, but as she had had stomach trouble since childhood, she had always had to be careful about over-eating She liked coffee, but it made her dizzy As a child she had had vomiting spells and dizziness She was always fond of comfort and fine clothes, but she believed that she did not care for affectionate displays

The patient always kept busy and active She said that as a child she always "tried to take everything in" She liked excitement, but was never able to stand it She was sick after seeing Barnum's circus She had rather frequent emotional discharges (temper tantrums) after which she would have a headache She was not extremely aggressive, but would not be considered timid

The patient's demand for sexual gratification was moderate, and her heterosexual adaptation in general was only fair Still she was not particularly fond of her own sex, and would rather work for a man

Self-Estimate The patient was quite confident of her own abilities She was not very suggestible She was rather self-sufficient, she did not seek company, though she did not shun it She was inclined to be somewhat reticent and evasive in a first contact, but seemed quite frank later She was generous

The patient was not unduly bound by principle or by a sense of loyalty She left her employers without much cause and she had no religious or social duties that she considered very important She was inclined to be stubborn

Mood The patient had no very distinct mood She said that she was inclined to be pessimistic, but that she used to be optimistic Her mood was fairly stable She said that she was pouty and sulky as a child She took a long time to get over real sadness, but stopped crying easily She said that she never forgave a wrong She was inclined to be worrisome and irritable She is rather easily frightened and

got palpitation and chilly sensations while this occurred. She did not perspire. She had fainted from fright at times. She was rather impulsive.

Adaptation Imperative. The patient was not very ambitious, courageous or inclined to lead. She derived her deepest satisfaction from the love of her son. She liked theaters, dining out and music. She used to enjoy outings in the country, but had not been on one for eight years. She was not religious or interested in social work or politics. She read very light fiction (cheap love stories).

This woman, like the one in case 17, enjoyed games and playing with boys. She successfully supported herself after her husband's death. She preferred to work with men and was a successful executive. Her marital and sex adjustments were not good.

CASE 19 (31557) —*Gastric Ulcer (Lesser Curvature, P O)*

Personal History.—The patient's birth and early development were probably normal. At 13 years she had rheumatic fever and was ill for fourteen weeks. She went to work at sewing when 13 or 14 years of age. She recalled that a man chased her for some immoral purpose when she was 13 or 14. She said "I was so frightened I couldn't speak." She had little chance for social life between 18 and 25 years of age. Her gastric symptoms dated back about forty years, or to when she was about 20 years old.

The patient married at 35, she knew her husband ten years before she married him. Her married life was not particularly happy, she said she married twice. She had had no sex knowledge till the age of 14. Sexual adjustment was very difficult, and she had great difficulty with her labors.

Personality.—The patient was fairly quick to learn. She was good at mathematics and history, but disliked geography. She was inclined to be somewhat distractible in conversation, though she was very intense in her concentration. She was certainly not inclined to day dream or to be introspective. Her auditory memory was fair, her visual memory, poor, and experience memory, good.

The patient was matter of fact in her attitude toward the usual things of life, and her judgment was good. She, however, did not plan well, but took things as they came to her. She had never been able to save money. She was handy with tools and had been an excellent seamstress.

She was naturally a hearty eater, but had had gastric difficulty so long that she had become a careful eater and avoided meat and spices.

The patient was fond of attention. She was inclined always to be active, "on the go," probably overactive, enthusiastic and somewhat aggressive. It would seem that her sex differentiation was not complete. She never adapted well and declared that she would never marry if she had to do it over. She had been a good deal of a tomboy and loved outdoor games to the exclusion of dolls.

The patient was quick in her reactions. She showed embarrassment easily. Her reaction to painful stimuli was markedly rapid and exaggeratedly fearful. She was rather easily suggestible. She was gregarious, and became lonesome easily. She was inclined to be confidential and apparently was not very reticent. She was generous to a fault.

The patient would be classed as an intuitive extrovert. She was not bound by principle and was not loyal. She was somewhat of an opportunist. She was usually happy but quite changeable. She was quickly excitable, she was not inclined to brood or worry. She was rather aggressive.

The patient had many recreative activities. She enjoyed music and the drama, but disliked reading. She hated the movies. She was not particularly religious or inclined to politics. She had little tendency to control her appetites.

This woman is matter of fact and handy with tools. She is unusually active and aggressive for a woman. As a child she was a "tomboy" and spurned dolls. Her two marital experiences were not good, and her whole sexual adjustment was difficult.

The following excerpts further illustrate the point under discussion.

Gastric Ulcer Females—The following cases are typical of the type mentioned.

CASE 20—The patient was married at 21 years of age. Her husband died young, leaving her with four small children. By doing waitress and chamber-maid work, she had managed to support the family very well. The educational opportunities were such that she was not fitted to do other work. She said, "I work too fast, my reason tells me one thing and my emotions another. I have never had time for the usual good times of woman." She was never interested in remarrying. She was the youngest child of a large family, and a difficult stepmother situation colored her early childhood.

CASE 21—The patient was married at 24 to a man younger than herself. This patient showed unusual control over her emotions. Her feeling was suppressed by reason. She assumed a protective role toward her husband. She was very proud of her expert tailoring abilities. (This woman was of the thin type, but her general appearance was quite feminine.)

Duodenal Ulcer Female—The following case is typical of the type mentioned.

CASE 22—The patient hated the idea of being a girl and so well adapted herself to a male role that her brothers were always willing to take her hunting and fishing with them. She spent her spare time in the carpentry shop of her father. She married at 17 years. The family made the match. The marriage was distasteful to her. Her husband died when she was 20 years old and left her with two small children. As a housekeeper in wealthy homes she had supported herself and the children. She had been called on for a good deal of executive work. She claimed that she had many opportunities for remarriage, but had never been interested. Her daughter was a pathetic, flat chested old maid school teacher, who had apparently never been allowed to have much life of her own, but had rather followed the dictates and plans of the mother. The patient was quite masculine in appearance.

If one contemplates the qualities perceived in the morphologic panel and in the case histories and excerpts, it is not difficult to see that the males present a surprising number of feminine attributes and the females much masculinity. These conditions have been so striking and are so closely related to sex reversibility and dualism that it has seemed best to discuss these phenomena separately. The following section deals with the androgynous mosaic and especially with the psychologic reactions that arise within the individual because of it.

THE ANDROGYNOUS MOSAIC

The strange and perplexing aspect of femaleness within the male and maleness within the female is, of course, not new. The circumstance of androgyny has long been recognized, not only by biologists and philosophers, but, generally, by most people. In discussing the matter of sex reversibility and duality within the same person, Oscar Riddle¹⁴ wrote

In general it can be said that whenever the "primary" sex characters (gonads) are reversed, the "accessory" and "secondary" characters are reversed also. For the reason that the primary sex character usually develops or differentiates earlier than do the so-called secondary ones, it happens that reversals occur more often and more readily in the secondary than in the primary characters. At once, therefore, we face the hard won fact that genetic (chromosomal) difference normally decides prospective sexuality, primary and secondary, but that this chromosomal difference is not the real or ultimate cause of sex difference—since usable agencies may secure either sex from the same chromosomal complex.

A little further on, after a discussion of the distribution of X and Y chromosomes, the following statement appears

The difference in kind is often visible in the sex chromosomes (X and Y) and sex determination normally follows the distribution of X and Y, it is not chromosomes as such, however, but genes carried in all chromosome-autosomes and sex-chromosomes that exercise this influence upon the origin and development of sexuality. This genetic complex, whether prospectively male or female, contains also a numerous minority of genes predisposed to the formation of the opposite sex. cytology has thus discovered and provided a basis for bisexuality in the individual.

In human beings there are plenty of examples of sex reversibility. Thus for instance, virilism in the female has been described by Gallais,¹⁵ Holmes¹⁶ and others in association with tumors of the suprarenal gland. The observations of Riddle¹⁴ on pigeons and doves, of Finlay¹⁷ on fowls and of Meisenheimer¹⁸ and Hegner¹⁹ on insects add further support to the belief that there is a definite sexuality of the soma which is expressed in the secondary characters of the individual regardless of the presence or character of the gonad. In this connection attention may be called to our earlier suggestion²⁰ that in those maladies in which one sex is definitely more often affected than

14 Riddle, Oscar. Factors in the Development of Sex and Secondary Sexual Characteristics, *Physiol Rev* **11** 63, 1931

15 Gallais, A. Le syndrome génito-surrénal, Paris, 1912

16 Holmes, G. *Quart J Med* **18** 143, 1925

17 Finlay, G. F. *Brit J Exper Biol* **2** 439, 1925

18 Meisenheimer, J. *Geschlecht und Geschlechter* Jena, Gustav Fischer, 1921, vols 1 and 2

19 Hegner, R. W. *The Germ-Cell Cycle in Animals*, New York, The Macmillan Company, 1914

20 Draper, G. The Influence of Sex upon the Constitutional Factor in Disease, *New York State J Med* **25** 1065 (Dec 1) 1925

the other, the selective susceptibility may very well be looked on as a secondary sex character. The effect of this curious arrangement on the behavior of those species which respond, without calculation, to the pressure of instinct is definite enough in respect of the attitude of one sex toward the other. Indeed, when a sex reversal is achieved experimentally, the somatic secondary sex characters always change, but so does the animal's psychology as displayed in modified conduct and demeanor. Thus there seems to be little question that sex reversibility and duality in the individual are biologic facts, not only in the lower animals, but also in man.

In man, however, the situation becomes infinitely complex because of his elaborate psychologic structure. Not only is he forced to make satisfactory (i. e., life-preserving and perpetuating) adaptations to the physical universe, but likewise he is continually driven to the task of establishing and maintaining an adequate adjustment of his personal, inner "man-environment unit." This psychologic unit is composed of his own idealized ego with its satellite emotions and the environment projected by his phantasy. In the life of primitive man, it is clear that physical strength and spiritual determination were the surest guarantees of security amidst the many dangers of his surroundings. Consequently, the virile attributes were especially desirable. They are the qualities that give to their possessors power over both animate and inanimate nature. The individual, man or woman, who holds such power obviously has a better chance of survival than the one who lacks it. If this be true then maleness must form the biologic foundation on which rests the instinct of self-preservation. In comparison, femaleness is incomplete, inadequate. This conception of the significance of maleness and the relative insignificance of femaleness has an important bearing on many psychologic problems that arise in the lives of human beings, and especially those that relate to the phenomenon of androgyny.

In almost all animal species many more male than female embryos are started. Thus, in the human species, it has been shown that for every 100 aborted female embryos there are 160 males. At term, from 104 to 106 living males are born for every 100 females. But at the end of the first year, there are 103 living females for every 100 males. It would seem, therefore, that the other instinctive urge, namely, that of race preservation, put a higher value on females than on males.

Femaleness thus appears to be essentially concerned with the safety of race or species, just as maleness is with that of the individual or self. But the problems presented to physicians by disease primarily concern the safety of the individual. Possibly it is for this reason that the perception of the female compound of the androgynous mosaic is often so disturbing to human beings. A man who possesses that degree of femaleness

which threatens the authenticity of his essential maleness becomes subject to deep-rooted, unconscious fears lest he fail in his attempt to play successfully the masculine rôle in life. Sometimes the recognition of the magnitude of this female component may have been vaguely or sharply recognized in consciousness, as it was by the patient in case 1. But even in that instance, the consciously presenting or vocalized fear was of homosexuality, although the dreams spoke otherwise. More often the fear of masculine failure has not reached consciousness at all and finds vicarious expression in violent efforts to display unusually virile capacities of mind and body and in the erotic conquest.

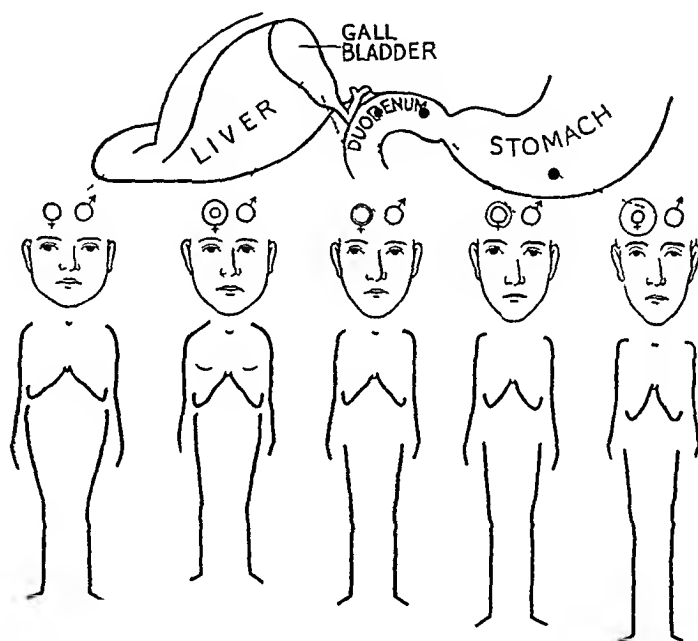


Fig 8—Distribution of male and female components in peptic ulcer and gallbladder people

In the case of the female the mechanism is practically the same. If there is any difference it is more in degree than in kind. The histories and excerpts showed that among the women there was a strong trend toward independence of action in life, desire to dominate and direct the course of others and to assume responsibility. In addition, they all reported a distinct lowering of sexual interest.

Figure 8 presents schematically our conception of the distribution of the male and female component in relation to gallbladder disease and peptic ulcer. It will be observed that the most feministic contours are found in the gallbladder individuals and that these gradually disappear through the series until they are least noticeable in the gastric ulcer. The sex symbols above the figures are intended to suggest the relative proportion of male and female in the individual, and it will be

observed that there is a diminishing amount of femaleness in the direction of the gastric ulcer person. But the psychologic reaction of these persons to their unconscious perception of their female component is apparently in inverse ratio to the actual content as indicated. This increasing reaction, which is actually the fear that the male has for the feminine component, is indicated by the circles with an increasing diameter juxtaposed to the sex symbols. This mechanism is reflected in the increasing ratio of females to males among duodenal, pyloric and gastric ulcers, respectively, which was previously referred to in St John's⁶ report. The figure on the extreme left represents the person with pernicious anemia. This individual is nearest to the neuter or species type. It is referred to the liver because of the relationship between the liver and blood-forming mechanism which has recently been demonstrated. With this brief explanation of the figure the reader will, on completing a perusal of the case histories, be able to perceive further significance in the diagram.

Attention might also be called to the fact that among duodenal ulcers a far greater number of patients begin their symptoms before the age of 25 than is the case among gastric ulcers. Thus Blackford and Dwyer²¹ found that in a series of 250 cases 50 per cent of the duodenal group reported that their symptoms began before the age of 25. In the gastric group less than 25 per cent showed symptoms before the age of 25 years. The most natural time in his life for a man to sense the threat of a too great feminine component is at the end of adolescence. It is then that he is approaching the moment when he will have to take his place in the competitive world and begin to assume the full responsibility which falls to the lot of the male. Among the gastric group, in which the female component is less marked, it is not so apt to be appreciated until the full pressure of an adult male's responsibility falls on him.

At this point it is not only of historical interest but also of aid in comprehending these mechanisms to refer to Freud's²² writings on the subject of human psychosexual development. He pointed out that in very early childhood the clitoris and penis are analogous in respect of their erotogenic sensibility. Furthermore, the evidence of sex differentiation in attitude and behavior appears early in the greater shyness, modesty and timidity of girls. At puberty in boys the urge toward sexual activity and prowess is augmented in association with the rapidly increasing size of the external genital organs and the physical strength of the muscles generally. On the other hand, in girls the onset of

²¹ Blackford J, and Dwyer, M. Peptic Ulcer. A Clinical Study of 250 Cases, *Tr Am Gastro-Enterol*, A 29 112, 1927.

²² Freud, S. *Drei Abhandlungen zur Sexualtheorie*, ed 5, Leipzig, Franz Deuticke, 1922, translated by A. A. Brill, New York, 1910.

menstruation and the obvious failure to develop further and convincing evidence of what has been a more or less successful identification comparison with the male increase the protecting walls of shyness and modesty. Evidence of having been outstripped in vigor, not only by demonstration of muscular strength, but also through the symbolism of virile sexuality, is overwhelming. In the face of these handicaps, many young women, especially in this day of general interest in athletics, resent the fact of their femaleness. This attitude is well illustrated by the case of a patient whose menstruation did not begin until she was 19 years old, and who, up until the age of 35, notwithstanding her unusually feminine appearance, still resented being treated chivalrously by men and more than anything else feared lest she play the rôle of clinging vine. Freud's basic observation and theory that the individual's psychologic reaction to life begins as male in both sexes and is subsequently arrested at puberty in the female go far to explain the intense effort of males to repudiate any suggestion of femaleness within them, and of females to strive to achieve and hold some evidence of residual maleness. Adler²³ subsequently seized on this thesis and elaborated it into his new well known concept of the "masculine protest."

The importance of the androgynous mosaic in determining the constitutional reaction to environment is therefore very great. On the one hand, it influences the immediate physical reactions of the individual to his palpable environment, and, on the other, profoundly affects his subjective psychologic interpretations of life experience. The creative force that we blindly call "mother nature" seems to be chiefly occupied with the continuation of the life principle, with the maintenance of species. She is not concerned at all with the fate of the individual. The latter must look out for himself by his own effort. For nature's purpose, then, females, among bisexual forms at least, are evidently more valuable than males. Femaleness displays a lower metabolic rate, is anabolic and represents conservation generally. It follows from this premise that in producing a male creature nature is moving further from her fundamental pattern than when she produces a female, thus the male individual is more widely differentiated from the species type than is the female. For this reason, it is not impossible that males possessing a very high degree of femaleness are more common than females with great masculinity.

Psychologically, however, the individual male cannot accept his female component with equanimity. The main exception to this seems to be in the case of the male of the gallbladder race. The degree of femaleness in such men is expressed very strongly in the soma as well

²³ Adler, A. *The Neurotic Constitution*, 1912, translated by R. Glueck and I. E. Lind. New York, Moffat, Yard & Company, 1917.

as in the psyche. Consequently, he seems to be less in conflict, and thus better able to accept the feminine component. His disease is anabolic. The significant difference between the males of the gallbladder and ulcer races, therefore, is one of psychic or emotional reaction to the feminine component. The gallbladder male accepts it, the ulcer male denies it. From this conflict arises the fear in the subconscious mind of the potential ulcer patient that when the crucial test comes he will fail to play the masculine rôle successfully. This elemental emotion, which might well be termed the essential male fear, forms a continuously present and active substratum of apprehension. The amount and intensity of that foundation obviously vary depending on the actual balance of the opposite sex qualities within the individual, and also on his constitutional sensitiveness to the threat of the female component.

Superimposed, then, on this chronic layer of anxiety is the acute or precipitating fear occasioned by the transient menace to life limb or ego. This is produced by the shocks so frequent, for example, in the lives of taxi drivers, bank messengers and persons whose occupations are such that a mistake means the loss of position by dismissal.

But the questions may well be asked whether this androgynous conflict is not present in all human beings, and if so why do not many more, if not all, people have ulcers? Quite obviously the phenomenon of androgyny is common to all persons, although the amount and distribution of the opposite sex component vary. Thus in a primary male the secondary female inclusion may be expressed wholly in one of his four panels of personality, or scattered between two or more. Still more important, however, is the person's subjective psychologic reaction to the feminine attributes. This is determined by his constitutional type. The specific response of a person to an emotion such as fear or anger is as much an expression of his constitution as is his reaction to bacterial or chemical insult.

The mechanisms that have just been discussed are active in the deeper levels of the mind, far below conscious thinking. For this reason they cannot be approached directly by explanation and argument. Some patients can be helped and even cured through the indirect attack of various forms of suggestion therapy or reeducation. But in our experience there are growing indications that in the principles of analytic psychology are to be found the ways to explanation and cure of all the functional disorders of the gastro-intestinal tract. However, a discussion of the relative value of different methods of psychologic diagnosis and therapy does not properly belong in this communication. Rather has the attempt been made to show that an intimate study of the "man-environment unit" may be at least as illuminating as are the investigation and treatment of the diseased organ itself.

SUMMARY

Unlike those medical investigations in which definite proof can be offered, the present study is concerned with phenomena that do not lend themselves to absolute determination. Yet there are important diagnostic and therapeutic implications contained in the correlations of total personality studies with recognized psychologic complexes and certain functions of the endocrine glands and the sympathetic nervous system.

To summarize, then, it may be said that the ulcer race families seem to produce a preponderance of males, and that these males are of the long thin type. Furthermore, not only in their morphology, but also in their psychologic make-up, they display a well marked emphasis on the feminine component of the androgynous mosaic. Fear, which is clearly an important factor in the digestive disturbance of the gastric ulcer race, is of two sorts. First, there is the chronic substratum of anxiety due to the person's constitutional sensitiveness to the threat of the female component. This is the elemental emotion which results in the masculine protest. Second, there is the acute or precipitating fear occasioned by the accident or insult which provides a transient menace to life, limb or ego.

It would seem that the peptic ulcer race was composed of persons of definite constitutional type. These people possess qualities of soma and psyche which can be easily recognized. When the healthy balance of the "man-environment unit" is disturbed symptoms in the domain of the sympathetic nervous system and gastro-intestinal tract develop. The "man-environment unit" disturbance can often be corrected permanently by the use of appropriate psychotherapeutic methods. Analytic psychology at present seems to offer the best attitude of approach.

EFFECT OF LIGATION OF THE PAROTID DUCT ON THE CARBOHYDRATE METABOLISM OF TOTALLY DEPANCREATIZED DOGS

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AND

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In another study,¹ the results of ligation of the parotid duct on the carbohydrate tolerance of normal dogs were reported. In these animals, it was found that the tolerance for dextrose, as determined by the blood sugar curve following the intravenous injection of dextrose solution, was definitely increased by ligation of the parotid ducts. As a step in the study of the mechanism of this action, the effect of ligation of the parotid duct was determined in a series of totally depancreatized dogs. Mansfeld and Schmidt² found that after partial extirpation of the pancreas (Sandmeyer diabetes) the resulting disturbances in carbohydrate metabolism were greatly relieved by ligation of the parotid ducts. In one animal in which the entire pancreas had been removed they were unable to detect any improvement following ligation of the parotid duct. Seelig³ found that ligation of Stenson's ducts did not prevent animals from dying after pancreatectomy. Extirpation of the pancreas, however, in animals in which the parotid ducts had previously been ligated, did not result in as high blood sugar values as were obtained in those in which the salivary ducts had not been occluded. Furthermore, these animals exhibited better wound healing than did those without ligation of the duct, and they did not suffer the characteristic, rapidly progressive cachexia of pancreatectomized dogs. In a few earlier, inconclusive experiments, we found that ligation of the parotid ducts in no way affected the rapidly downward course of dogs following total extirpation

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* From the Metabolic Laboratory of the Department of Physiology, Nelson Morris Institute for Medical Research, Michael Reese Hospital

1 Zimmerman, Leo M. Effect of Ligation of the Parotid Duct on the Carbohydrate Tolerance of Normal Dogs, *Arch Int Med* **49** 409 (March) 1932

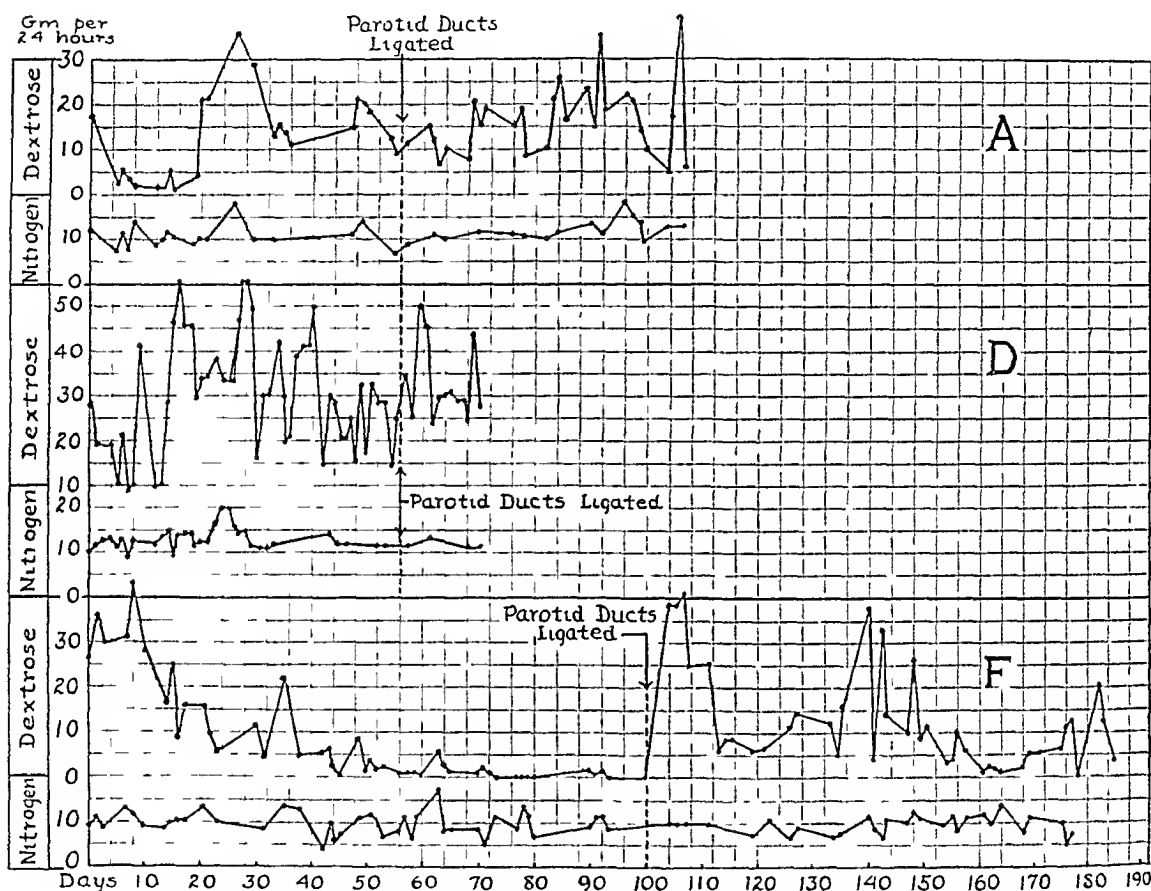
2 Mansfeld, G, and Schmidt, E. Versuche zu einer operativen Behandlung des Diabetes, *Klin Wchnschr* **7** 1457, 1928

3 Seelig, S. Ueber Beziehungen zwischen Parotis, Pankreas, Blutzucker und Diabetes mellitus, *Klin Wchnschr* **7** 1228, 1928

of the pancreas. In the experiments to be described here careful metabolic studies were made in a series of three dogs that had recovered following total pancreatectomy. After an adequate period of observation, the parotid ducts were ligated, and the studies were continued.

METHOD

Completely depancreatized dogs were used for this work. The animals were allowed to recover completely from the operative procedure with the aid of insulin,



Curves showing the excretion of dextrose and nitrogen before and after ligation of the parotid duct in three animals A, D and F.

and presented well healed, noninfected wounds. They were maintained on a meat sugar, raw pancreas and insulin regimen throughout these experiments. In each case the diet and insulin were kept as constant as possible throughout the entire period of observation. The amount of insulin used in the different experiments was graded, so as to maintain different levels of glycosuria in the different animals. After a control period of from two to three months, both parotid ducts were ligated under a brief ether anesthesia and observations were continued as before. Dog F was followed for almost three months after the ligation was performed. Twenty-four hour specimens of urine were collected at intervals throughout each experi-

ment and analyzed for nitrogen by the Kjeldahl method, and for dextrose by the Somogyi⁴ modification of the Schaffer-Hartmann technic. The results are presented in graphic form in the accompanying chart.

COMMENT

In the accompanying chart, which shows the excretion curves in three animals, both before and after ligation of the parotid duct, it is noted that the dextrose output is fairly uniform. The curve is apparently more constant in the animal that was kept at a low level of glycosuria than in those with a higher excretion of dextrose. The nitrogen output is uniform, and serves as a check for the excretion of dextrose. There is no striking change in the level of glycosuria as a result of the ligation of the parotid duct. It would therefore seem that ligation of the parotid ducts has no effect on the carbohydrate metabolism of totally depancreatized animals.

These results, which coincide with others reported, as mentioned earlier in the paper, would indicate that the factor that increases the carbohydrate tolerance of normal dogs as a result of ligation of the parotid duct is incapable of action when the pancreas has been removed. This suggests that it is not primarily an insulin-like action, but that it operates through the pancreas, possibly in a stimulating or activating manner. The failure of its action in the pancreatectomized animal does not prove, of course, that the operation would be without effect in cases of diabetes in human beings.

CONCLUSIONS

Ligation of the parotid ducts exerts no demonstrable effect on the carbohydrate metabolism of totally depancreatized dogs. The factor that is responsible for the increased dextrose tolerance following ligation of the parotid ducts in normal animals, therefore, probably does not have a direct, insulin-like action, but rather operates through the pancreas as an activating or stimulating agent.

⁴ Somogyi, M. A Method for the Preparation of Blood Filtrates for the Determination of Sugar, *J Biol Chem* **86** 655 (April) 1930.

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO STAPHYLOCOCCUS ALBUS

REPORT OF A CASE ¹

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It is my endeavor to present the clinical, bacteriologic and pathologic findings as well as the daily progress in a case of subacute bacterial endocarditis due to *Staphylococcus albus*, with a view toward the further study of the disease caused by this group of bacteria

The clinical and bacteriologic manifestations of subacute bacterial endocarditis have been carefully studied and described by a large number of clinicians, both in this country and abroad In a study of 5 cases, Schottmuller ¹ found *Streptococcus mitior* (*viridans*) as the cause of this type of bacterial endocarditis In a study of 97 cases of subacute bacterial endocarditis, Horder ² found 62 due to streptococcus, 19 due to *Staphylococcus aureus*, 5 to influenza bacilli, 3 to gonococcus and 1 to streptococcus and staphylococcus Osler's ³ study of 10 cases, in 6 of which cultures of the blood were taken, showed negative results in 3, streptococcus in 1 and staphylococcus in 1 In the exhaustive studies of Libman and Celler, ⁴ as well as in Libman's ⁵ later studies of the atypical forms of subacute bacterial endocarditis, during which positive cultures were obtained, the bacteria most frequently found as the cause was *Streptococcus viridans* Lenhartz, ⁶ in his study of 37 cases, found 19 due to streptococcus, 9 to pneumococcus, 7 to *Staphylococcus aureus*, 1 to gonococcus and 1 to *Staphylococcus albus* Clawson, ⁷ in a study of 46 cases, found 34 caused by streptococcus, 5 by pneumococcus and 7 by *Staphylococcus aureus* In his report on cases of subacute bacterial endocarditis from the Johns Hopkins Hospital, Thayer, ⁸ found the

¹ Submitted for publication, July 27, 1931

1 Schottmuller *Munchen med Wchnschr* **57** 617, 1910

2 Horder, T J *Quart J Med* **2** 289, 1909

3 Osler, W *Brit M J* **1** 467, 1885

4 Libman, E, and Celler, H L *Am J M Sc* **140** 516, 1910

5 Libman, E, and Sacks, B *A Hitherto Undescribed Form of Valvular and Mural Endocarditis*, *Arch Int Med* **33** 701 (June) 1924

6 Lenhartz *Munchen med Wchnschr* **482** 1178, 1901

7 Clawson, B J *An Analysis of Two Hundred and Twenty Cases of Endocarditis*, *Arch Int Med* **33** 157 (Feb) 1924

8 Thayer, William S *Johns Hopkins Hosp Rep* **22** 1, 1926

following groups among the 137 fatal cases that came to necropsy streptococcus, 60, Staphylococcus aureus, 26, pneumococcus, 26, gonococcus, 19, Staphylococcus albus, 4, pyocyaneus, 1, and anthracis, 1. These figures show that the streptococcus is the type of bacteria that most frequently produces subacute bacterial endocarditis. The bacteria next in frequency is Staphylococcus aureus, with pneumococcus and gonococcus following. Last comes Staphylococcus albus.

REPORT OF A CASE

History—E. F., a white girl, aged 16, was admitted to the People's Hospital, New York, on Feb. 4, 1931. She had had the ordinary diseases of childhood. Otherwise, the past history was unimportant. About six months prior to admission to the hospital, the patient was working hard and long hours, from 8 a. m. to 10 p. m. About four months before admission, she began to feel weak and became nervous and lost her appetite. She had pains in the joints of all the extremities, but there was no swelling. On Jan. 21, 1931, two weeks before admission to the hospital, the patient was sent to the country, where she contracted a cold and cough with pain in the chest and occasional headaches. She became more pale and nervous. She returned to the city and was admitted to the hospital. The chief complaints on admission were pain in the chest, cough and asthma.

Physical Examination—The patient was well developed, markedly pale and somewhat emaciated. The skin was moist and clear, no rashes or petechiae were seen. The pupils were equal and reacted to light and in accommodation, the conjunctivae were clear and pale. The mucous membrane of the mouth was pale, the tongue coated, the pharynx slightly congested and the tonsils small and cryptic. No pus could be expressed from them. The ears were normal. The heart was moderately enlarged, a loud systolic murmur was heard at the apex and was transmitted over the entire cardiac area to the left axilla posteriorly and to the interscapular region. Examination of the lungs revealed normal resonance, vesicular breathing and no râles. The abdomen was soft, with no area of tenderness, the liver and spleen were not palpable. The extremities were normal, the patellar reflexes were normal, there was no Babinski or Kernig sign. The genitals were normal.

Course—On admission, the temperature of the patient was 102 F., the pulse rate, 132, the respiratory rate, 24, and the blood pressure 110 systolic and 60 diastolic. The patient appeared comfortable and did not complain of anything except asthenia. Roentgen examination of the chest gave normal results. During the patient's stay at the hospital, the temperature ranged from 99 to 104.2 F., the average being between 101 and 103 F.

February 16. The patient complained of pain in the left forearm. The temperature rose to 103.2 F. Examination showed no areas of redness or swelling. The tenderness was along the muscles of the painful area.

February 19. Physical examination showed the cardiac condition about the same. The spleen was moderately enlarged but not tender, and was felt about 1 inch below the free border of the ribs. No petechiae were found.

February 25. The patient complained of pain in the finger-tips. There was no swelling or tenderness in any of the joints of either hand.

March 4. A transfusion of 350 cc. of blood was given by the Unger method.

March 5 The patient had a slight chill during the night which lasted about two minutes, and she coughed at times. Reexamination gave negative results.

March 14 The patient vomited, appeared drowsy and complained of pain in the joints.

At intervals of a few days thereafter she showed the following symptoms: weakness and pain in the muscles of the right leg, increasing apathy, no desire for food, twitching of the facial muscles and aphasia.

A second transfusion was performed, 400 cc. of blood was given, this had no effect. Her condition became gradually worse, incontinence developed followed by hemiplegia on the right side and dysphagia.

On March 30, the patient went into coma, and petechial hemorrhages appeared on the conjunctiva of both lower eyelids.

Her condition became progressively worse, and she expired on April 2.

Laboratory Data—Cultures of the blood on February 4, 5 and 17 gave negative results after ninety-six hours. A culture made on February 28 was positive for *Staphylococcus albus* after ninety-six hours. Positive cultures for the same organism were again obtained on March 11 and 24, after seventy-two hours.

Hospital Chart of Laboratory Observations

Date	Total Red Blood Cells	Hemoglobin, per Cent	Total White Cells	Polymorpho-nuclears, per Cent	Large Mono-nuclears, per Cent	Small Mono-nuclears, per Cent	Basophils, per Cent
February 4	1,920,000	40	12,000	76		24	
5	1,930,000	40	15,500	71	10	19	3
19	2,260,000	45	14,600	88		12	
28	2,250,000	43	14,000	89		10	1
Band Form							
March 3				39			
5	2,000,000	46	10,200	91		9	
7	3,629,000	37	6,900	90		10	
24	1,700,000	26	6,000	93		7	
30	1,203,000	23	5,300	96		4	

In order to eliminate all possibility of contamination, the culture made on March 24 was taken in the operating room prior to the transfusion of blood.

Daily urinalysis showed an average specific gravity of about 1.022, albumin, 4 plus, no sugar and no acetone or diacetic acid. Microscopic examination showed hyaline and granular casts but no red cells.

Necropsy—Autopsy was performed on April 2. Cultures from the pericardial fluid showed a growth of colonies of *Staphylococcus albus* after three days. A culture of valve vegetation showed a growth after seven days. Transplanted smears showed *Staphylococcus albus*.

The heart, lungs, kidneys, spleen and liver were examined.

Macroscopic examination disclosed numerous petechial hemorrhages seen on the parietal and visceral pericardium. Near the apex of the left auricle there were adhesions between the visceral and parietal pericardium which were easily broken. The pericardial fluid was increased.

There was dilation of the right side of the heart, with hypertrophy of the left. The mitral valves were almost entirely destroyed by ulcerations, and were replaced by fragile vegetations of various sizes. The cusps were fused and narrowed. On the wall of the left auricle there was a small area of vegetation. The other valves were normal.

The pleural cavities were clear. The left lung was adherent to the wall of the chest. There were no areas of consolidation. The right lung was the seat of numerous infarcts, some of which had broken down and were surrounded by red areas of consolidated lung tissue.

The liver appeared normal. The spleen was markedly enlarged, and showed a number of infarcts, some old and healed, others fresh and white.

On section, the left kidney showed scarring from old infarcts.

Microscopic examination of the lungs showed chronic congestion with scattered areas of lobular pneumonia.

The spleen showed congestion and edema, infarction with beginning fibrosis.

The kidneys showed congestion and edema of the tubules.

The heart showed ulcerative endocarditis, the muscles of the heart showed scattered areas of round cell infiltration. No Aschoff bodies were present.

Bacteriologic examination of stained tissues showed all organs to be negative for bacteria, except the vegetation of the valves which contained gram-positive cocci in groups, but no chain formation.

SUMMARY

Clinically, this case bears such close resemblance to the type of subacute bacterial endocarditis caused by the *Streptococcus viridans*, as described by Libman and Cellar⁴ and by Libman⁵ in his later studies of the atypical forms, that the clinician may easily be misled in diagnosing this case and classifying it as one caused by the *Streptococcus viridans* were it not for the blood cultures. There are, however, in this case, a few clinical points which differentiate it from the cases described by Libman.

Although on several occasions the patient complained of pain in the joints and muscles, at no time was there any visible swelling, redness or heat changes in the disturbed parts. There were no corresponding changes in temperature that would be expected with such conditions. At no time during the patient's stay at the hospital could subcostal tenderness be elicited. Petechial hemorrhages did not appear until three days before death, although embolic phenomena appeared in other parts of the body.

The appearance of the patient suggested severe anemia but there was not the *café au lait* color described by Libman.

This case differed clinically and pathologically from the cases described by Thayer.⁸ In all of his cases there was a known focus of infection. Of the four cases described, the first was a mixed infection with typhoid intestinal hemorrhages, the second was a case of pulmonary tuberculosis with cavities of the lungs, syphilitic aortitis and chronic valvular lesions, the third was a case of pulmonary tuberculosis and encapsulated interlobar empyema, and the fourth was of acute onset following paronychia with high temperature and all other symptoms of an acute infection. In this case the white blood count was 44,000. The patient died in twenty-three days. In all of his cases the observations

on the blood and the hemoglobin percentages varied markedly from those of the case herewith reported. The red blood counts ranged from 3,604,000 to 3,761,000. The hemoglobin percentages were between 63.6 and 64.3. In three of the cases, the white blood count was between 8,000 and 10,000. With the exception of one case, the duration was from three to four months. The myocardial changes were insignificant. Pericarditis was not observed. The vegetations in the valves were large, except in the case of typhoid fever.

The case described by Lenhartz⁶ varied from the case reported in that the onset was acute, following trauma, and the course was short.

Dr. Held, Dr. Diamond, Dr. Dubovsky and Miss Gold, the laboratory technician, gave assistance and suggestions in this work.

CHOREA GRAVIDARUM

A STATISTICAL STUDY OF 951 COLLECTED CASES, 846 FROM THE
LITERATURE AND 105 PREVIOUSLY UNREPORTED

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AND

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WASHINGTON, D C

(Concluded from page 533)

CLINICAL COURSE

Month of Onset of the Chorea—The available material has been carefully studied with respect to the month of pregnancy in which the chorea first manifested itself. Data on this subject were available in 670 cases. The choreic attack preceded the pregnancy in 38 cases. It developed in the first trimester in 312 cases, in the second in 219 cases and in the third in 101 cases, including 2 cases in which the attack began during labor and 1 case in which it began on the second day post partum. The distribution of the onset by months is graphically indicated in chart 4. By a rather rough approximation, it will be seen that one half of the attacks are initiated in the first trimester, one-third in the second and one-sixth in the third.

Duration of the Attack and Time of Recovery or Death—More difficulty was experienced with the accuracy of the data on this point than in any other phase of the study, and the figures to be given are approximations in the majority of instances.

Considering first the nonfatal cases, it was found that in 565 pregnancies the chorea ceased ante partum in 167 cases, intra partum in 1 and post partum in 361, and it was reported to have continued indefinitely post partum in 36. The material was also studied with the view of determining whether or not there was any difference in the proportion of patients recovering ante partum or post partum according to the month of pregnancy in which the attack began, but no particular difference was found. It is worthy of note, however, that in only 1 case in which the chorea was present before conception did recovery occur during pregnancy, while in 18 such cases recovery did not take place until after delivery.

There were 118 cases in which recovery from chorea took place prior to delivery and in which a more or less accurate estimation of the duration of the attack could be made. Study of these cases gave the following results: 1 attack lasted two days, 1, one week, 1, two weeks

1, three weeks, 31, one month, 37, two months, 23, three months, 7 four months, 6, five months, 7, six months, 1, seven months, and 2, eight months, an average duration of two and one-half months. There were 234 cases available for the study of postpartum recovery. The duration of the attacks prior to delivery was as follows: less than one month, 34 cases, one month, 45, two months, 28, three months, 30, four months, 26, five months, 15, six months, 22, seven months, 17, eight months, 17. On assigning an arbitrary value of two weeks for the cases lasting less than one month, there is an average duration prior to delivery of three and three-tenths months. In 132 of these cases, the time elapsing from delivery to recovery was found to be as follows: 1 attack ceased during labor, 1 in three hours, 4 "immediately", 1 in one day, 5 in a "few days", 18 in less than seven days, 44 in the second week, 14 in the third week, 15 in the fourth week, 21 in the second month, 3 in the third month, 1 in the fifth month, 2 in one year,

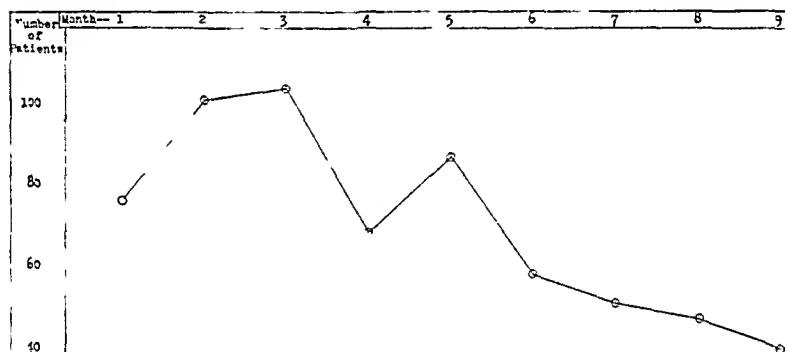


Chart 4—Month of pregnancy in which choreic attack began in 592 cases

1 in eighteen months, and 1 in three years. Excluding the cases lasting one or more years, the average postpartum duration of the attacks was about twenty-two days. Eleven additional cases in which the chorea began during pregnancy were reported to have continued post partum indefinitely. This material was also studied to see if any relation could be traced between the duration of the attack before and after delivery, but no such relationship could be found.

In turning attention to the duration of the fatal cases, it is found that 21 patients died undelivered after attacks lasting three, twelve and sixteen days, and one and three weeks in 1 case each, one month in 5 cases, two months in 7 cases, and three months in 4 cases, thus, the average duration of these twenty-one attacks was one and one-half months. In 41 cases terminating fatally post partum, the antepartum duration of the choreic attacks was two days in 2 cases, less than one month in 12 cases, one month in 9 cases, two months in 7 cases, three months in 6 cases, four months in 3 cases, and six and seven months

in 1 case each, an average antepartum duration of one and six-tenths months. In 24 cases terminating fatally postpartum, the interval between delivery and death was one day or less in 5 cases, two days in 9 cases, three, five, six, eight, ten, eleven, twelve, fourteen and a "few" days in 1 case each and one month in 1 case. In the last case, the chorea ceased two weeks postpartum, but the patient died of acute endocarditis two weeks later. On eliminating this case and the one lasting a few days, in 22 cases the average time elapsing between delivery and death was about four days.

From these figures it will be seen that the average duration of attacks terminating during pregnancy in either recovery or death is two and one-half and one and one-half months, respectively, the average antepartum duration of attacks terminating in postpartum recovery or death is three and three-tenths and one and six-tenths months, respectively, and the average time elapsing between delivery and postpartum recovery or death is twenty-two and one-tenth and four and one-tenth days, respectively.

These findings may be compared with those of the report of the British Collective Investigation Committee (Mackenzie) for ordinary chorea. Their data covered the duration of 398 cases, of which 71 lasted less than one month, 133 between one and two months, 95 between two and three months, 44 between three and four months, 32 between four and six months and 23 over six months. For comparison with the cases during pregnancy, these figures represent an approximate average duration of between two and three months. It will be seen that the total pregnant cases tend to run a shorter course than this, that the cases in which recovery occurs during pregnancy coincide closely, and that, as might be expected, the cases in which postpartum recovery occurs average approximately twice the duration of the controls. There is certainly no striking divergence between the pregnant and the non-pregnant cases to be detected here.

Chorea Recurring in More than One Pregnancy—Repeated attacks of chorea, the data on which are given in table 1, are of considerable interest and importance. There were 253 choreic pregnancies in 99 patients, 69 patients had 2 choreic pregnancies, 18 had 3, 7 had 4, 4 had 5 and 1 had 13, an average of 2.5 choreic pregnancies for each patient. The distribution of these in the various pregnancies is given in table 8.

With respect to the course of the chorea in these cases before and in the interval between pregnancies, it is interesting to note that in about two thirds of the 99 cases the reports were sufficiently accurate to show the complete cessation of the chorea between pregnancies, and this was true with proportionate frequency in the cases giving a history of chorea before the first pregnancy and those giving none. It is also of interest to note that in the case of one patient (186 table 1) who had

never had chorea prior to pregnancy the disease continued post partum, complicated 3 pregnancies and, apparently, continued indefinitely after the third. In another case the patient (199, table 1) had never had chorea or rheumatism before the attack of chorea in her first pregnancy. The intervals between the first 3 pregnancies were free from chorea, although it recurred in all. Following the third pregnancy the chorea continued, complicated the fourth pregnancy, and then continued until the patient's death at 68 years of age. Altogether there were 16 instances in which chorea occurred for the first time during pregnancy, was absent in the interval between and recurred in subsequent gestations, in 3 instances, 5 times.

TABLE 8—*Distribution of Choreia in Various Pregnancies in Same Patient*

Numerical Order of Pregnancies Complicated by Choreia	Number of Cases
First and second	51
First and third, second free from chorea	2
First and fifth, second, third and fourth free from chorea	1
First and thirteenth, others free from chorea	1
Second and third, first free from chorea	5
Second and third, first unknown	1
Second and sixth, others unknown	1
Second and one other, number unknown	1
Third and fourth, first and second free from chorea	1
Third and fourth, first and second unknown	1
Two pregnancies, order unknown	4
First, second and third	12
First, second and fourth, third free from chorea	3
Second, third and fourth, first free from chorea	1
Third, fourth and fifth, first and second free from chorea	1
Three pregnancies, order unknown	1
First, second, third and fourth	5
First, second, fifth and sixth, third and fourth free from chorea	1
Four pregnancies, order unknown	1
First, second, third, fourth and fifth	4
First to thirteenth, inclusive	1

The Effect of Choreia on Pregnancy—This may be studied from the data in 646 cases. In 314 of these, or 48.6 per cent, pregnancy was uninterrupted and was terminated by spontaneous labor at term. Of the remaining 332 cases, pregnancy was artificially terminated in 171 instances and spontaneously prematurely in 161. The spontaneous interruptions were caused by premature labor in 63 cases, by abortion in 64 cases, occurred at an unknown period of pregnancy in 1 case, by rupture of an ectopic pregnancy in 1 case, and by death of the mother undelivered in 32 cases.

SYMPTOMS

Movements—It will be unnecessary to go into any detailed consideration of the symptoms. The characteristic hypermotility and incoordination are pathognomonic and, as is pointed out by many observers, differ in no particular and are indistinguishable from those of Sydenham's chorea. The movement is mostly general. In the more severe

cases the patient is constantly in motion, and the incoordination is so extreme that she is absolutely incapable of doing anything for herself. During sleep the movements usually cease.

Fever —The disease is usually afebrile. Fever, when it does occur, is of ominous significance, and hyperpyrexia may occur, the temperature was 109.6 F. in 1 fatal case and 108 F. in another, with recovery.

Blood Pressure —The blood pressure is not altered. In 14 different observations, the systolic range was from 136 to 99.

Urine —The condition of the urine was mentioned in 97 cases, albumin was present in 42 and absent in 55 instances. The presence of casts is occasionally noted.

Blood —Blood cultures were negative in 3 instances, and in 1 *Staphylococcus aureus* was isolated. The chemical status of the blood is reported to have been normal in 1 observation. In the febrile cases, a leukocytosis seems to be generally present, in 8 observations the range was between 28,500 and 8,000.

On comparing these symptoms with those of Sydenham's chorea, it will be seen that the characteristic hypermotility and incoordination are identical. Further, there are present no symptoms or laboratory findings that in the slightest degree indicate the presence of any ordinary toxemia of pregnancy, with the possible exception of the albuminuria, which, however, is frequently noted in an otherwise normal pregnancy and would be expected to be present occasionally in a condition of a presumably infectious origin.

COMPLICATIONS

The most frequent complications are acute psychoses, probably usually of the intoxication exhaustion type, acute endocarditis and acute rheumatic fever, all of which are identical with those of Sydenham's chorea and are considered more in detail elsewhere. Eclampsia occurred in 6 cases, which, considering the fact that 320 pregnancies were definitely stated to have gone to full term, would seem to be without special significance. Three cases were complicated by hysteria and 2 by epilepsy. In 1 fatal case there were convulsions followed by coma and hemiplegia, probably of embolic origin.

DIAGNOSIS

The diagnosis offers no difficulties and is usually self-evident. Hysteria might occasionally have to be eliminated, as in the case of pseudochorea of hysterical origin reported by Marshall. Royston considered 1 of his cases to be possibly one of pseudosclerosis. Roques, in a recent article entitled "Epidemic Encephalitis in Association with Pregnancy, Labour and the Puerperium," devoted 113 pages to an

exhaustive consideration of this subject. His study of 21 cases has led him to differentiate definitely between epidemic encephalitis in pregnancy and chorea gravidarum. He stated that the latter is characterized by a previous history of chorea or rheumatism or both, rheumatic nodes, cardiac complications, a greater tendency to spontaneous interruption of pregnancy and the occurrence earlier in pregnancy and more frequently in primiparae. He also gave the mortality of encephalitis complicating pregnancy as 42 per cent in 170 cases, which, as will be shown later, is almost 3 times greater than that of chorea gravidarum.

PROGNOSIS

In table 9, the mortality rates for various groupings of the cases are presented in such form that they may be seen at a glance. These findings will now be considered in detail.

General Mortality—Figured on the basis of the number of deaths in persons having 1 or more choreic pregnancies, the results were 613 recoveries and 136 deaths, a mortality rate of 18.1 per cent in a total of 749 patients. In these 749 patients, for whom the result was known there occurred a total of 902 reported pregnancies, and in these the patients survived in 766 instances and died in 136, a mortality rate of 15 per cent for pregnancies. These rates are based on a series of cases almost twice as large as any previously collected and one from which in marked contrast to most previous series, all duplication has been eliminated. It is interesting to observe, therefore, that they indicate a general prognosis less gloomy than the estimates heretofore usually given, which have ranged around 25 to 33.33 per cent. Further study of the figures tends to reveal an even better prognosis.

Mortality Considered Chronologically—Thus when the cases are arranged in three groups, according to the date of their reporting, namely, those reported prior to 1880, from 1880 to 1899, inclusive, and from 1900 to date, periods roughly corresponding to what may be termed the preantiseptic, antiseptic and aseptic eras in obstetrics, we find a steady decline in the mortality rates, as follows: preantiseptic era, 124 pregnancies, with 31 deaths, a mortality rate of 25 per cent; antiseptic era, 237 pregnancies with 36 deaths, a mortality rate of 15.1 per cent, and aseptic era, 541 pregnancies with 69 deaths, a mortality rate of 12.7 per cent.

Mortality in Relation to the Previous History Regarding Chorea and Rheumatism—It is interesting to find how figures based on this large series of cases lend support to the opinion so frequently expressed, particularly in the French literature, that chorea in more than 1 pregnancy or in a patient giving a history of chorea before pregnancy, is less fatal than the single isolated attack that constitutes the first choreic

seizure It is, of course, evident that in order to have chorea in more than 1 pregnancy the patient must survive it in at least 1, but, on the other hand, it might be possible and even might be expected, *a priori*, that more patients would ultimately die after several attacks than after one This is not borne out by the facts, which show 10 deaths in 94 patients having 2 or more choreic pregnancies, a mortality rate of 10.6

TABLE 9—Comparative Mortality Rates for Various Groups of Cases

	Total No of Cases	Total Lived	Total Died	Mor- tality Rate
General mortality				
By individuals	749	613	136	18.1
By individuals, two or more choreic pregnancies for each	94	84	10	10.6
By pregnancies	902	766	136	15.0
Mortality chronologically				
Prior to 1880—preantiseptic era	124	93	31	25.0
1880 to 1899, inclusive—antiseptic era	237	201	36	15.1
1900 to date—aseptic era	541	472	69	12.7
Mortality in relation to previous history of chorea and rheumatism				
History of chorea prior to first choreic pregnancy	219	203	16	7.3
No history of chorea prior to first choreic pregnancy	177	145	32	18.0
History of rheumatism prior to first choreic pregnancy	133	125	10	7.4
No history of rheumatism prior to first choreic pregnancy	229	198	31	13.5
History of both chorea and rheumatism prior to first choreic pregnancy	95	89	6	6.3
History of neither chorea nor rheumatism prior to first choreic pregnancy	110	89	21	19.0
Mortality in relation to age by hemidecades				
15 to 19 inclusive	138	119	19	13.7
20 to 24 inclusive	324	267	57	17.5
25 to 29 inclusive	122	97	25	20.4
30 to 34 inclusive	34	28	6	17.6
35 to 39 inclusive	9	8	1	11.1
Mortality in relation to time of onset of the chorea in pregnancy				
Chorea present before pregnancy	34	34	0	0
Onset of chorea in first trimester	292	244	48	16.4
Onset of chorea in second trimester	207	173	34	16.4
Onset of chorea in third trimester	98	79	19	19.3
Mortality in relation to psychotic complications	49	41	8	16.3
Mortality in relation to fever	26	3	23	88.4
Mortality in relation to the manner of termination of pregnancy				
Spontaneous terminations of pregnancy				
At term	312	306	6	1.9
By premature labor	63	55	8	12.6
By abortion	64	49	15	23.4
By rupture of ectopic pregnancy	1	1	0	0
Total of spontaneous premature terminations	128	105	23	17.9
By death of patient undelivered	32	0	32	100.0
Total of spontaneous premature terminations, including deaths undelivered	160	105	55	34.3
At an unknown period of pregnancy	1	0	1	100.0
Total of all spontaneous terminations, excluding deaths undelivered	441	411	30	6.8
Total of all spontaneous terminations, including deaths undelivered	473	411	62	13.1
Artificial terminations of pregnancy				
By induction of labor at term	6	3	3	50.0
By induction of premature labor	37	27	10	27.0
By induction of abortion	94	68	26	27.6
By induction at an unknown period	5	2	3	60.0
Total of all cases of induction	142	100	42	29.5
By vaginal hysterotomy	11	8	3	27.2
By abdominal hysterotomy	9	6	3	33.3
By accouchement force	7	0	7	100.0
By vaginal hysterectomy	2	0	2	100.0
Total of all cases of operative delivery	29	14	15	51.7
Total of all artificial terminations of pregnancy	171	114	57	33.3
Mortality chronologically, artificial terminations of pregnancy				
Prior to 1880—preantiseptic era	4	2	2	50.0
1880 to 1899, inclusive—antiseptic era	39	24	15	38.4
1900 to date—aseptic era	128	88	40	31.2
Fetal mortality	537	268	269	50.9

per cent In a group of 219 cases giving a positive history of an attack of chorea prior to any choreic pregnancy, there were 16 deaths, a mortality rate of 7.3 per cent with which there may be contrasted a rate of 18 per cent in a group of 177 patients whose histories failed to disclose any chorea previous to the attack during pregnancy

In 135 pregnancies in which there was a definite history of previous rheumatism there were 10 deaths, a mortality rate of 7.4 per cent, with which may be contrasted a rate of 13.5 per cent in a group of 229 pregnancies in which the histories positively denied any previous rheumatism In the group of 95 cases giving a history of both chorea and rheumatism previously there were 6 deaths, a mortality rate of 6.3 per cent, with which may be contrasted a rate of 19 per cent in a group of 110 cases giving a history of neither chorea nor rheumatism

It will be seen from these findings that there is a definitely lessened mortality in patients who have had chorea or rheumatism previously and a still lower rate in those who have had both In seeking the explanation for these facts, the most obvious recourse would seem to lie in the direction of some immunologic mechanism—the explanation is difficult on any other hypothesis

Mortality in Relation to Age—It will be seen from table 9 that in the first three hemidecades of sexual maturity the mortality increases with the patient's age, while in the fourth and fifth it drops sharply, the exact mortality rates being as follows 15 to 19, inclusive, 138 cases with a mortality of 13.7 per cent, 20 to 24, 324 cases, with a mortality of 17.5 per cent, 25 to 29, 122 cases, with a mortality of 20.4 per cent, 30 to 34, 34 cases, with a mortality of 17.6 per cent, and 35 to 39, 9 cases, with a mortality of 11.1 per cent The rise in the rate for the first three hemidecades seems to be quite definite and what might be expected from the generally accepted fact that the mortality of ordinary chorea is less in children than in adults The sudden drop in the next two hemidecades is even more definite and, at first glance, would seem to be an unexpected finding It might be explained, however, by considering two points, namely, that at these more advanced ages none of the women have had previous chorea either with or without association with pregnancy, which, as we have seen, tends to diminish the mortality and, also, that there is more likelihood of error in a diagnosis of chorea gravidarum made at this time of life, when ordinary chorea is so rare as to be a medical curiosity

Mortality in Relation to the Time of Onset in Pregnancy—The data available for the study of this subject are from a total of 631 cases, and the results obtained were as follows onset of chorea before pregnancy, 34 cases with no deaths, onset in first trimester, 292 cases with 48 deaths, a mortality rate of 16.4 per cent, onset in second tri-

mestel, 207 cases with 34 deaths, a mortality rate of 16.4 per cent, onset in third trimester, 98 cases with 19 deaths, a mortality rate of 19.3 per cent. It will be seen that there is so little difference in the mortality rates for the various trimesters of onset of the chorea that the conclusion would appear to be justified that this factor is without influence. The striking absence of mortality in the group of 34 cases in which the onset of the chorea antedated the pregnancy is in line with the previously noted lower mortality rate in cases giving a history of previous chorea and is probably to be explained through the establishment of a relative immunity before conception.

Mortality in Relation to the Manner of Termination of the Pregnancy—For this study data were available in a total of 644 pregnancies. As might be expected, the most favorable manner of termination is by spontaneous labor at term. In 312 such cases there were only 6 deaths, a mortality rate of 1.9 per cent. In 63 cases with spontaneous premature labor there were 8 deaths, a mortality rate of 12.6 per cent, and in 64 cases of spontaneous abortion there were 15 deaths, a mortality of 23.4 per cent. Altogether, including the case in which recovery occurred following the spontaneous rupture of an ectopic pregnancy, there were 23 deaths in 128 cases in which pregnancy was spontaneously prematurely interrupted, a mortality of 17.9 per cent. If, however, we add to these figures 32 patients who died undelivered we have a group of 160 cases in which pregnancy was terminated by the death of the woman undelivered, or by spontaneous premature labor or abortion, with a total of 55 deaths, a mortality of 34.3 per cent. If we include the cases of spontaneous labor at term and 1 fatal case with a spontaneous termination of pregnancy at an unstated period, there is a group of 473 cases in which the pregnancy was not artificially interrupted, of these, 62 died, giving a mortality rate of 13.1 per cent for conservative management of the complicating pregnancy.

Turning now to the cases in which pregnancy was artificially terminated at varying periods and by various methods, we find as follows. In 6 cases in which labor was induced at term there were 3 deaths, a mortality rate of 50 per cent, induction of premature labor, 37 cases with 10 deaths, a mortality rate of 27 per cent, induction of abortion, 94 cases with 26 deaths, a mortality rate of 27.6 per cent, induced interruption, period not stated, 5 cases with 3 deaths, vaginal hysterotomy, 11 cases with 3 deaths, a mortality rate of 27.2 per cent, abdominal hysterotomy, 9 cases with 3 deaths a mortality rate of 33.3 per cent, accouchement forcé, 7 fatal cases, vaginal hysterectomy 2 fatal cases. Altogether, therefore, we have a group of 171 cases in which pregnancy was artificially terminated, with 57 deaths a mortality rate of 33.3 per cent. A critical examination of the case reports in this

group with the view of determining the number of deaths directly or indirectly due to postpartum infection immediately disclosed the impossibility of arriving at any definite figures. It may be said, however, that there is definite evidence that infection played an important part, and this is borne out by a chronological grouping of the cases, which shows 4 pregnancies artificially terminated prior to 1880, with 2 deaths, a 50 per cent mortality, 39 cases from 1880 to 1899, inclusive, with 15 deaths, a 38.4 per cent mortality, and 128 cases from 1900 to date, with 40 deaths, a 31.2 per cent mortality.

There can be no question that the medical profession has shown little or no tendency toward an unwise radicalism in resorting to therapeutic abortion or induction of premature labor in handling chorea gravidarum. On the whole, one gets the impression that the cases so handled have been wisely selected. This being granted, and taking a mortality of 31.2 per cent as representing what may be expected from this procedure, under modern conditions, that is, in the group artificially terminated since 1899, we find for comparison a mortality rate of 17.9 per cent in 128 cases in which there was a spontaneous premature interruption of pregnancy. It would seem only fair, however, to add to this latter group the 32 cases in which the pregnancy was terminated by the death of the mother undelivered, resulting in a mortality rate of 34.3 per cent. Thus it will be seen that in a group of 288 cases serious enough to result in the death of the mother undelivered or in spontaneous premature interruption of pregnancy, on the one hand, and to indicate to the physician the advisability of artificial, aseptic termination of pregnancy, under modern conditions, on the other, we find a difference in mortality of only 3.1 per cent in favor of intervention.

Mortality in Relation to Psychotic Complications—Acute mania and other psychoses, delirium, etc., are noted as complicating the choreic pregnancy in 51 cases, in 49 of these in which the result for the mother is given, there were 8 fatalities, a mortality rate of 16.3 per cent. This is so little in excess of the general rate for choreic pregnancies, 15 per cent, that it would seem to indicate a less gloomy prognosis for this complication than is generally conceded in the literature. In several of these cases, however, the psychoses continued post partum, and in some instances the patients ultimately died in hospitals for the mentally defective.

Mortality in Relation to Fever—It is to be regretted that the majority of the reports are so fragmentary as to make exact deductions difficult on many points. This applies to the incidence of fever. In many cases the context clearly indicates that fever must have been present, yet it is not mentioned. There is a group of 27 cases, however, in

which the presence of fever is specifically mentioned, or, from the context, it is evident it must have been present during the choreic attack. Of 26 of these patients for whom the result was known, 3 lived and 23 died, a mortality rate of 88.4 per cent. This finding strongly confirms the statement of French and Hicks that fever is of the gravest prognostic import.

Fetal Mortality—The fate of the fetus was either mentioned or could be safely inferred from the context in 537 cases, it survived in 268 instances and died in 269, a fetal mortality rate of 50.9 per cent. A detailed study of these figures seems unnecessary. In about 200 of the 269 fetal fatalities, the pregnancy was interrupted either spontaneously or artificially before the period of viability, or the woman died undelivered. In 79 cases of spontaneous or induced premature labor in which the fate of the child was mentioned, there were 37 deaths. It will be seen, therefore, that prematurity is decidedly the predominating factor in the large fetal mortality rate.

Two babies born with chorea promptly recovered.

There has been a tendency in the literature to differentiate chorea gravidarum from Sydenham's chorea because of its supposedly higher mortality. It will be seen from the mortality statistics just presented that the rate is not nearly so high as has generally been given and that, since 1900, it has been 12.7 per cent. In speaking of the high death rate of chorea during pregnancy, Dakin pertinently said: "Whether this is due altogether to the existence of pregnancy or whether the danger is common to all adults whether pregnant or not, the present cases are not sufficiently numerous to determine, but it is usually believed to be more dangerous to those in the gravid condition." He reported from St. George's Hospital, London, 2 deaths from chorea in 18 nonpregnant women, and Mackenzie reported 1 death in 77 such cases, a total of 3 deaths in 95 cases, a rate of 3.1 per cent. This may be compared with Mackenzie's rate of 1.8 per cent in 432 cases of Sydenham's chorea without pregnancy, but including males and females of all ages. From these figures it would seem that Dakin's question must be answered to the effect that Sydenham's chorea is appreciably more dangerous in the nonpregnant woman than in the child, but that adult chorea is from three to four times more fatal with pregnancy than without it. This, however, is certainly insufficient ground on which to base a differentiation between these two types of chorea. Many examples immediately come to mind notably that of influenza, illustrating the increased mortality of certain diseases during pregnancy. It must also be borne in mind that the pregnant woman with chorea has, in addition to the hazard of the disease, all the dangers incident to a pregnancy predisposed to premature interruption spontaneous or

induced. These hazards of pregnancy are undoubtedly responsible for some but not all of the increased mortality. It would seem reasonable to believe that the factors responsible for the remaining increase must be sought in some breakdown of resistance comparable to what may be believed to occur in influenza.

Dakin's additional statement that chorea gravidarum "is certainly much more common in adult women who are pregnant than in those who are not" is not borne out by combining his own and Mackenzie's statistics, which show that of 109 cases of chorea in women of child-bearing age, 14 were pregnant and 95 were not. These figures are of importance in showing that pregnancy is by no means the only etiologic factor responsible for chorea in the adult.

TREATMENT

The consideration of treatment naturally divides itself into the question of the treatment for the chorea and the proper management of the pregnancy.

The former of these subjects will first be briefly reviewed from the historical standpoint. The use of chloroform by inhalation with the idea of controlling the hypermotility would seem to be the worst possible procedure. Several authors pride themselves on their faithfulness in continuing this for days, relays of medical students being employed to render it possible. The last case in which such treatment was used was as late as 1906. The result was 7 deaths and 1 recovery in 8 such cases. In the same category is the use of very large doses of morphine. There is good evidence for believing that an overdose of morphine was directly responsible for 1 fatality and for suspecting that it contributed to a few others. The older idea of a reflex origin of the chorea is evidenced by such procedures as applications of iodine to the cervix, or its dilatation, incision of the hymen for the relief of dyspareunia and excision of a urethral caruncle, all of which were believed to have been beneficial and even to have produced cures. Much more rational would seem to be the clearing up of foci of infection by tonsillectomy or the extraction of septic teeth reported to have been of benefit in a few cases. Haneborg thought he got great benefit from the use of thymus gland in 1 case. Arsphenamine or sodium cacodylate were used in a few cases, apparently merely as a more modern method of administering arsenic. Magnesium sulphate intramuscularly was used in 1 fatal case. On the hypothesis of a pregnancy toxemia, blood serum from a pregnant woman was employed in 3 cases, 2 of which were fatal. Selitzky employed repeated injections of normal horse serum in 3 cases with no deaths.

In looking at the subject from the point of view of modern knowledge of chorea or, possibly more truthfully, admitted lack of

knowledge, and in accepting as a working basis the hypothesis of the absolute identity of chorea gravidarum with Sydenham's chorea, we may now consider the best modern management of both the chorea and the pregnancy

With respect to the chorea, it would seem to be safe to admit that we are without any treatment that even approaches specificity and are therefore reduced to a purely symptomatic therapeutics. It is certainly extremely doubtful if the time-honored use of arsenic, either as solution of potassium arsenite or in more modern form, has much effect on the disease, and personally we believe the same may be said for the salicylates. Shaw, of Manchester, claimed good results from large doses of thyroid, which, however, we believe may be equally attributed to the sanity and conservatism of the balance of his method of management. As has been stated he and also Pinaud and Rudaux hold practically identical views in attributing the chorea of pregnancy to gestational toxemias, and, based on this assumption, they advocate rest, isolation, promotion of elimination and a milk diet. The last two authorities employ chloral to effect a depressant action on the nervous system. While the evidence here adduced would seem to justify the conclusion that their etiologic assumption is without any sound basis, their treatment would seem admirably to meet most of the requirements of the situation in the present state of knowledge, and certainly no other method yields better results. The matter of diet is probably open to some question, and one that was bland, nutritious and easily digested, with an abundance of fluid, would probably be more rational than milk alone. Hypnotics other than chloral are, of course, available, particularly the substitution products from barbituric acid. In our own case the judicious use of morphine was certainly helpful in gaining rest and quiet, but Wall and Andrews are undoubtedly right in warning against large doses of these potent drugs. Another important indication to be met is preventing the patient from injuring herself by accidental falls and blows.

When these simple measures fail to bring about improvement, or even to arrest the course of the disease toward greater and greater severity, the question of therapeutic abortion must be met. It is difficult to determine on a fair standard of comparison between the results of intervention and nonintervention as shown by these statistics. A group of 473 cases in which pregnancy was not artificially terminated gave a mortality of 13.1 per cent as against a rate of 33.3 per cent for a group of 171 cases in which it was so terminated. The first group, however, includes 312 pregnancies that progressed to full term with a mortality of only 1.9 per cent, in these cases the chorea quite obviously, was in a mild form. It would seem fairer, therefore, to make the comparison between the group of 160 cases in which the pregnancy was spontane-

ously terminated prematurely or resulted in the death of the woman undelivered and the group of 171 cases with artificial terminations, these two groups may be considered as equally made up of the more serious and fulminating cases. The respective mortality rates are 34.3 and 33.3 per cent, a balance in favor of intervention of only 1 per cent. The latter group, however, contains 7 fatal cases in which accouchement forcé was employed, 2 fatal cases in which vaginal hysterectomy was performed and 6 fatal cases of 20 in which the delivery was by vaginal or abdominal hysterotomy. Since the judgment shown in the selection of these methods of procedure would seem open to considerable question, we have eliminated them, and thus have remaining a group of 137 cases in which pregnancy was terminated by induction of labor, prematurely or at term, or therapeutic abortion. In table 10 we have made a chronological comparison between the respective mortality rates resulting from intervention and nonintervention in these two groups.

TABLE 10—*Chronological Comparison of Mortality Rates with and without Therapeutic Abortion or Induced Premature Labor**

	Without Intervention				With Intervention			
	Total No of Cases	Total Lived	Total Died	Mor- tality Rate	Total No of Cases	Total Lived	Total Died	Mor- tality Rate
Prior to 1880	35	13	22	62.8	3	2	1	33.3
1880 to 1899, inclusive	43	30	13	30.2	37	24	13	35.1
1900 to 1919, inclusive	43	30	13	30.2	33	21	12	36.3
Since 1919	39	32	7	17.9	64	51	13	20.3

* Cases going to full term and operative deliveries have been excluded.

Study of these figures discloses, we believe, only two generalizations that may safely be made. First, that since 1919 there has been a sharp decline in the mortality rate both with and without intervention, and, second, that, excluding the 3 cases in the intervention group prior to 1880 as being too small a number to justify comparison, the group with intervention shows a 6.1 to 2.4 per cent greater mortality. From the statistical point of view, therefore, it will be seen that there is no evidence favoring the interruption of a pregnancy complicated by chorea.

Statistical evidence alone, however, is notoriously untrustworthy, and it is thought, therefore, that the question of intervention or nonintervention should be considered further in the light of the evidence adduced in this paper as to the true relationship between the pregnancy and the complicating chorea. We think that it has been conclusively demonstrated that chorea is not a direct complication of pregnancy, but that either the association is a purely accidental one, or, possibly more frequently, the pregnancy acts by reducing resistance to a disease previously present in latent form. The situation would seem to be most comparable to the occurrence of pregnancy in a person with latent or

inactive tuberculosis. In deciding whether or not to intervene, other factors entering into the prognosis should receive careful consideration. On the one hand, the undoubted tendency of pregnancy to prolong the attack, the clinically well attested likelihood of prompt recovery post partum and the triply or quadruply greater mortality during pregnancy, on the other, the lack of mortality in the cases in which the onset of the chorea precedes the pregnancy and the uniformly favorable prognosis in cases giving a history of a previous attack of chorea or rheumatism, or both. We get the impression that the time of intervention has a direct bearing on its efficacy, and that little may be hoped from therapeutic abortion undertaken in the presence of high fever, leukocytosis, petechiae of the skin and other evidences of active infection. One might as well expect favorable results from therapeutic abortion in such acute medical complications as influenza, typhoid, pneumonia or acute endocarditis. Because of this reasoning, we do not accept these symptoms as indications for intervention, as advocated by Pinard and, also, by LePage, and would consider them as best treated expectantly, for we know of no analogous situation in which intervention would be considered as indicated, and the result of intervention under these circumstances, as may be seen from table 1, is almost uniformly fatal. If this logic is sound, it necessarily follows that the time for intervention, if at all, is before such symptoms develop. If, then, despite a thorough trial of a treatment admirably summed up by Wall and Andrews as consisting of "rest, seclusion, careful feeding and gentle discipline," to which it would seem safe to add the judicious use of nerve sedatives, there is a steady progression in the intensity of the disease with constant and violent movement, incoordination of the muscles of speech and deglutition and intractable insomnia, and particularly if psychotic disturbance becomes evident, interruption of pregnancy should be seriously considered. As to the method of election, the results in this series speak eloquently. It would seem evident that under the circumstances involved there will always be time to employ the induction of abortion or premature labor rather than some form of operative delivery, and the advisability of this choice is evidenced by a mortality of 51.7 per cent in 29 cases delivered by vaginal hysterectomy, vaginal and abdominal hysterotomy and accouchement forcé. Exceptions to this rule might be noted in cases in very early pregnancy, in which a simple curettage would suffice, or, in the case of repeated choreic pregnancies, in which the abdominal route might be selected in order to effect sterilization.

SUMMARY AND CONCLUSIONS

This paper is a statistical study based on an analysis of the available data of 951 choreic pregnancies occurring in 797 persons, much the largest collection of cases thus far assembled. One case was personally

observed by us, and the remainder were collected from the literature or through the medium of a questionnaire sent to more than 500 American obstetricians

The disease is very rare. In 270,825 obstetrical hospital admissions from Europe, America and Australia, the incidence was 1 case in 2,275 pregnancies, in 115,554 similar admissions in the United States, the incidence was 1 case in 3,501, which undoubtedly gives an exaggerated idea of its frequency here since of 170 obstetricians replying to our questionnaire 113 had never seen a case.

Our study has led us to the definite conclusion that the chorea occurring during pregnancy is identically the same disease as Sydenham's chorea in adolescents, modified slightly, in certain respects, by its association with pregnancy. This opinion we believe to be positively supported by the following facts:

1. Women attacked are predominantly in the youngest age group of sexual maturity and are mostly primiparae.

2. More than one half of them give a history of a previous attack of an ordinary chorea, more than one third of them of a previous attack of rheumatism, more than one fourth of them have had both diseases previously and in about 1 case in 20 there is a double complication of acute rheumatic fever and chorea in the same pregnancy.

3. The statistics of Allard from the Baudelocque Clinic show that 25 per cent of women giving a history of adolescent chorea have a recurrence of the disease in subsequent pregnancies.

4. The mortality in the group of cases with a previous history of chorea is 7.3 per cent, with a previous history of rheumatism, 7.4 per cent, with a history of both diseases previously, 6.3 per cent. In the groups giving the opposite history, the rates are 18, 13.5 and 19 per cent respectively. These figures are impossible of explanation except on the hypothesis that a previous attack of chorea or rheumatism or both confers a relative immunity.

5. There is evidence of heart disease in about one third of the cases, and of cardiac pathology in 87 per cent of those coming to autopsy.

6. There is as much histopathologic evidence in the brain favoring the identity of the two conditions as there is opposed to this view, and there can be no question that in both, the blunt of the attack is borne by the corpus striatum.

7. The tendency of the disease to greater severity and a more prolonged course when complicating pregnancy would be expected, *a priori* and is in line with the behavior of other acute or chronic infectious processes under the same circumstances.

8. The symptoms and usual complications are identical.

The prognosis is much less grave than has hitherto been believed and seems to be improving as the mortality rate of 12.7 per cent since 1900 is one half of that obtaining prior to 1880

The best treatment for the chorea theoretically and from the standpoint of results obtained consists of "rest, seclusion, careful feeding and gentle discipline" (Wall and Andrews). Nerve sedatives and morphine may be used, but sparingly and with great discretion

In mild cases there is undoubtedly no reason for therapeutic abortion. In severe cases the statistical evidence fails to show better results with intervention than without, in fact, the reverse is true. If resorted to at all, intervention should be by the induction of premature labor or abortion and, except in rare instances, not by immediate operative delivery, as the mortality in these procedures is about 50 per cent. Its most likely indication would seem to be in the case in which the patient is getting progressively worse, despite treatment, but before fever, leukocytosis, etc., give evidence of active and generalized infection, under the latter circumstances, it apparently does nothing but hasten the fatal outcome

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ASSOCIATION OF INFECTIOUS ASTHMA AND ARTHRITIS

FROM THE POINT OF VIEW OF BACTERIAL ALLERGY*

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In a recently reported study of four hundred adults with asthma, 47 per cent were found to be insensitive to the usual soluble proteins. There was reason to believe that in this group the asthma was an expression of allergy accompanying infection resident in foci of the respiratory tract, in contradistinction to the other groups in which atopic hypersensitiveness, as well as infection, played a rôle. In the entire series of four hundred patients, there were nine in whom, in addition to asthma attacks of arthritis developed.

The ages of these patients varied from 36 to 59. Six were females and three, males. The character of the arthritis was migratory, affecting the wrists, fingers, shoulders, ankles, etc. It was accompanied by moderate redness and swelling and pain on motion, and sometimes persisted for several weeks. The body temperature was not elevated. With the exception of three of our cases in which roentgen examination revealed mild proliferative changes in one joint as a rule (the spine or knee), probably due to secondary static influences, no sequelae were noted in any other affected joints.

In five of these patients, foci of infection constituted the sole etiologic factors for the asthma as well as the joint manifestations. In the remaining four there was a coexistent atopic hypersensitiveness to substances such as ragweed, goose feathers, dog hair and rabbit hair, to foods and also to dust. Elimination of these atopogens alone influenced neither the asthmatic nor the arthritic attacks. Therefore it seemed that infection in the sinuses and lungs was the exciting cause of both the asthma and arthritis. This theory was proved by the fact that following the evacuation of pus from the infected antrums and the successful treatment of the diseased ethmoids, by means of tampons, mild silver protein, U S P, irrigation, etc., and after the recession of the more

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TABLE 1—*Association of Asthma and Arthritis*

Case	Age	Past History	Röntgenogram of Sinuses	Röntgenogram of Chest	Skin Tests	Arthritis	Treatment	Course and Results
1	17	Admitted 1/28/25, asthma 14 years throughout year	6/18/30, cloudiness of ethmoids and left antrum	Partial consolidation of lower lobe of right lung with considerable fibrosis due to an unresolved pneumonia	Ragweed, short	6/5/27, migrating polyarthritis for 8 weeks, "episodic" 6/18/30, arthritis recurred	Evacuation of pus in left antrum 6/18/30	Arthritis receded, asthma improved
2	51	Admitted 1924, asthma 20 years	Pansinusitis, 3/31/31, pansinusitis	Negative, clinical bronchitis	Negative	1/5/26, right shoulder, wrists, sacrum and spine, 3/3/31, recurrent polyarthritis	11/28/27, partial ethmoidectomy, sinuses infected	Arthritis subsided, well till 1930, under treatment for sinuses, 6/6/31, arthritis improved
3	49	Admitted 1922, asthma 13 years, worse in winter	Negative, purulent ethmoiditis clinically	Negative, clinical bronchitis	Goose feathers	Both knees and left wrist, 11/11/25	Irrigation and tampons	12/16/25, arthritis subsided
4	54	Admitted 9/2/27, asthma 18 years	Negative	Unresolved pneumonia	Feathers and dust	Right knee	Typhoid vaccine	Improved
5	36	Admitted 5/26/26, asthma 8 years	Ethmoiditis	Negative	Negative	3/16/28, poly arthritis	Local nasal treatment	6/6/28, arthritis receded, asthma improved
6	57	Admitted 6/6/28, asthma 6 years	Left antrum cloudy	Unresolved pneumonia in both lower lobes	Negative	Polyarthritis, neuralgia parasthetica, 9/12/28	Evacuation of pus from both antrums	Asthma improved, 2/20/29, arthritis receded
7	36	Admitted 5/3/26	Negative	Unresolved pneumonia lungs 4/6/28	Negative	7/27/27, shoulder, elbows, wrists and fingers, right scapula	Typhoid vaccine	3/12/28, remission of asthma, exacerbation of arthritis, 7/20/28, joints better, 8/12/29, no asthma, migrating arthritis, 8/28/30, asthma well, arthritis subsided, roentgenogram of chest negative
8	59	Admitted 6/5/25, asthma 50 years, pleuropneumonia 1919, influenza 1923, influenza 1929	10/19/27, pansinusitis 4/6/28	Unresolved pneumonia of base of left lung	Negative	11/11/27, polyarthritis, 12/7/28, arthritis left knee, spondylitis of thoracic spine	Evacuation of pus from antrum, typhoid vaccine	Arthritis and asthma improved
9	52	Admitted 2/25/31, asthma 4 years, 1918, bronchitis, 1927, asthma began	Cloudiness of right ethmoids at both antrums	Negative	Dog hair, rabbit hair, cat hair, foods	1917, polyarthritis, 1927, polyarthritis	Evacuation of pus from antrums	Improved during summer of 1918, asthma subsided 3/4/31, arthritis recurred

recent pulmonary focus of infection, the arthritis subsided completely in eight of the nine cases. The asthmatic attacks became milder and diminished in frequency, and the harrassing cough ceased almost entirely.

During the warm weather all residual symptoms referable to both conditions disappeared, indicating the general beneficent effect of temperature and climate on chronic respiratory infections and their complications.

Additional unusual features noted were episcleritis in case 1, diagnosed by the ophthalmologist as evidence of a "rheumatic diathesis," meralgia paraesthetica of the right leg in case 6, and sciatica on the right side in addition to the arthritis in case 7. Comparison of the duration of the asthmatic and arthritic manifestation are shown in table 2.

It is evident from table 2 that a number of years had intervened between the onset of the asthma and that of the joint manifestations.

TABLE 2—*Comparison of Asthmatic and Arthritic Manifestations*

Case	Age	Duration of Asthma	Duration of Arthritis
1	47	14 years	2 years
2	51	20 years	4 years
3	49	13 years	1 year
4	54	18 years	1 year
5	36	8 years	3 months
6	57	6 years	1 year
7	36	18 years	2 years
8	59	50 years	2 years
9	47	13 years	4 years

If one assumes that as in asthma, an allergic mechanism is accountable for arthritis, the explanation for the delay may lie in the prolonged period necessary to set this secondary shock tissue into action in a system in which the lung was the dominant primary shock organ. The occurrence of several shock tissues as the seats of allergic reactions is not uncommon in the human being. The ascendancy of one over another is equally frequent. Thus a patient who continually has asthmatic seizures from eating eggs may only occasionally have urticaria from the same agent. This is in contrast to the findings in the lower animals in which, as a rule, only one type of shock tissue is found. In the guinea-pig, it is always the pulmonary system, in the rabbit, the circulatory system, and in the dog, the liver is the so-called shock organ involved in anaphylactic reactions.

The transient suppression of one shock organ during the supremacy of another is further exemplified in cases 7 and 9, in which the asthmatic seizures alternated with the attacks of arthritis and vice versa. In case 7, in which both were due to residual pneumonic infiltrations, the recession of the pulmonary focus was succeeded by the subsidence of the asthma as well as the arthritis.

In case 9, the asthmatic attacks ceased following the treatment of the purulent antrums, but a fresh attack of arthritis of the great toe of the right foot brought this patient back to the clinic. In reviewing this case we found that, in addition to the sinus disease there was an underlying atopic hypersensitiveness to inhalants as well as to numerous foods, which in all probability was fundamentally responsible for the secondary infection. In 1914 the patient had an intranasal operation, but in spite of it he continued to contract so-called colds. In 1917, he had an attack of polyarthritis which lasted for three months.

With the onset of the warm weather the arthritis receded, but the nasal condition began to bother the patient again. This condition persisted until 1918, when so-called bronchitis developed, which lasted throughout the year until the winter of 1927, when a recurrence of arthritis occurred. Simultaneously the asthmatic attacks appeared for the first time. The arthritis again subsided with the return of summer. On the last admission he complained of asthma which, as already noted, was controlled after irrigation of the sinuses, only to be succeeded by the arthritis. Whether food sensitiveness plays an additional rôle in the arthritis of this patient or whether, as seems more probable, the sinusitis was incompletely eradicated it is impossible to state at present.

The striking sequence of events in these cases, the identification of a common focus of infection responsible for the asthma and arthritis and the elimination or recession of the infection being followed in most patients by amelioration of the asthma and disappearance of the arthritis leads us to the conclusion that both conditions are mediated by the same agent, and we suggest that a similar mechanism, namely, bacterial allergy, may be operative in both.

In examining this conception it is important to have a clear idea of what we mean by allergy and especially, bacterial allergy.

On account of its varied connotations, a definition of allergy is a most difficult task. To facilitate the understanding of its current status, a brief review of its evolution may be timely.

Originally employed by Pirquet¹ in 1906 to designate "Reaktionsfähigkeit" or the reacting capacity of actively sensitized and artificially prepared animals to the original antigen, it was used later by the same author to describe reactions of man to foreign substances. Cooke and Vander Veer² and Spain³ however, by careful clinical studies have been able to demonstrate that certain persons in this allergic group are radically different from normal persons, by heredity, and possess the

1 Pirquet, C. *Allergie*, München med Wchnschr **53** 1457, 1906, *Allergy*, Arch Int Med **7** 259 (Feb) 1911.

2 Cooke, R. A., and Vander Veer. *J Immunol* **8** 163, 1923.

3 Spain, W. C., and Cooke R. A. *J Immunol* **9** 521, 1924.

faculty of spontaneously reacting to foreign proteins, in other words they are naturally hypersensitive. Prausnitz and Kustner⁴ and de Besche⁵ found that the serum of such patients contains specific bodies (reagins) capable of sensitizing the normal human skin. Reagins of the same character have subsequently also been found in artificially sensitized patients. Nevertheless, Coca⁶ felt that in order to differentiate those artificially sensitized from those who are spontaneously sensitive, the latter should be designated as atopic.

As normal persons who do not possess atopic characteristics may on artificial contact with certain foreign substances, such as horse serum or bacterial proteins, acquire and manifest similar reactions, that is, reactions characterized by an anaphylactic-like mechanism seen in atopic patients or in animals, such persons may also be designated as allergic.

The term allergy for the present therefore, in contrast to atopy may serve as a generic term to indicate sensitiveness of the atopic and acquired type to foreign proteins, chemical substances and bacteria. Whether the ability to acquire sensitiveness is universal or requires a special predisposition is difficult to state with certainty. In view of the fact, however, that the same agent that induces allergic manifestations in one individual does not do so in another seems to imply that peculiar constitutional factors play a rôle.

These factors are evidenced not only in localized cellular tissues, but embrace the humoral as well as the neural structures, particularly the vegetative nervous system and its various ramifications.

In asthmatic persons the autonomic system is particularly vulnerable. The vagus and its reflex paths may so readily be affected by various exciting agents that the lung is readily thrown into shock. The occurrence of a similar phenomenon in the guinea-pig's lungs caused Doerr⁷ to call it "the shock organ." Coca,⁶ transposing this idea to the human being, designated tissue manifesting altered reactivity as "shock tissue." That in the atopic patient a single substance like shell fish may simultaneously induce reactions of several shock tissues, such as the lung, skin and joints, inducing asthma, urticaria and arthritis, is well known. Similar effects may follow in persons whose sensitiveness is acquired. To demonstrate such sensitiveness to soluble proteins by means of skin tests, etc., is comparatively easy. However, in dealing with chemical agents or bacteria, numerous difficulties present themselves.

4 Prausnitz and Kustner, H. *Centralbl f Bakt* **86** 160, 1921.

5 de Besche, A. *Am J M Sc* **166** 265, 1923.

6 Coca, A. F. *Atopy. The Newer Knowledge of Bacteriology and Immunology*. Chicago, University of Chicago Press, 1928.

7 Doerr, R. *Ergebn d Hyg, Bakt, Immunitätsforsch u exper Therap* **5** 71, 1922.

In the study of allergy to bacteria the question naturally arises What is it that sensitizes the individual, the whole organism, the so-called soluble specific substance, the somatic proteins or the toxins? It is obvious that the primary effects of toxins must be taken into account in interpreting results in disease in human beings Toxins have thus far not been proved to be responsible for allergic manifestations On the other hand, Wells⁸ made the suggestion that toxins may represent a combination of a pure toxic radical which does not give a positive reaction to chemical tests for proteins and attached proteins, and that such radicals may split off more or less completely from their particular protein vehicle and reunite with the proteins of the animals into which they are injected, thereby serving as a sensitizing antigen Analogies for this process may be found in the reactions taking place between nonprotein substances, such as iodine, salicylates, arsenic, etc., which are supposed to unite with the individual's own protein, thereby converting them into foreign proteins which serve as antigens Landsteiner's⁹ well known work with the azoproteins may serve as an example of such synthesis *in vitro*

Convincing proof, however, of the actual occurrence of such combinations with toxin is lacking As a matter of fact, the work of Zinsser and Grinnell¹⁰ and of Dochez and Stevens¹¹ tends to disprove such an antigenic rôle Dealing with streptococci, these authors were able to segregate a neutralizable toxin, and thus demonstrate that the hypersensitiveness obtained was due to a nonneutralizable bacterial product This naturally leads one to other bacterial products as sources of allergic reactions

In 1925, employing streptococci, Zinsser and Grinnell¹⁰ were able to sensitize guinea-pigs and subsequently elicit skin sensitiveness with streptococcus material, especially Dick filtrate, corresponding, in manner of production and in important attribute of heat stability, to tuberculin They suggested at this time that such streptococcus allergy might have some relationship to certain forms of arthritis in which the association of sterile joint conditions with streptococcus infection had been recognized clinically Sensitizing guinea-pigs with hemolytic streptococci as well as pneumococcus autolysates in 1927, these workers again were able to obtain skin sensitivity more severe than that seen in the most extreme reaction to tuberculin In a number of their guinea-pigs, when satisfactory skin sensitization had been obtained with the pneumo-

8 Wells, H. G. *The Chemical Aspects of Immunity*, New York, The Chemical Catalog Company, 1925

9 Landsteiner, K. *Biochem Ztschr* **104** 280, 1920, *J Exper Med* **39** 631, 1924

10 Zinsser, H., and Grinnell, F. B. *J Immunol* **10** 725, 1925

11 Dochez, A. R., and Stevens, F. A. *J Exper Med* **46** 487, 1927

coccus autolysate, this material injected into the joints caused the development of swollen joints, whereas in normal controls as well as in animals in which skin tests were negative, showing an absence of allergy, the joints were uninvolved. Zinsser and Grinnell felt that many substances analogous to their pneumococcus autolysates may be liberated from the bacteria within the infected body in the case of organisms not subject to test tube autolysis, and suggested that this process in the course of pneumonia might occur in the lungs and furnish sensitizing antigens in considerable quantities. If this is so, it may serve to explain the infectious asthma that we have described in association with unresolved pneumonia.

The more recent work of Francis and Tillet¹² has substantiated to a great extent the early observations of Zinsser and Grinnell. By injecting type-specific polysaccharides of the pneumococcus capsule intradermally into patients with pneumonia following the crisis, they were able to demonstrate definite cutaneous reactions in certain instances with carbohydrates homologous to the type of pneumococcus causing infection in the patient. The character of the cutaneous reaction is urticaria-like in appearance, and runs its course in one or two hours. The reaction caused by the pneumococcus protein, on the other hand, is similar in appearance and evolution to that evoked by tuberculin. Such positive reactions reach their maximum intensity within about twenty-four hours after injection and sometimes require from three to four days to subside completely. The capacity of the patient to react to the protein bears no relation to the type of pneumococcus causing the infection.

Fatal anaphylactic shock with nitrogen-free bacterial carbohydrates of pneumococcus types II and III in guinea-pigs passively sensitized with the precipitating serum of rabbits immunized with pneumococci of the homologous type has been obtained by Avery and Tillet¹³. Tomcsik¹⁴ and Tomcsik and Kurotchkin,¹⁵ isolating specific carbohydrate material from *B. lactis-aerogenes* found that the pneumobacillus and a yeast were likewise able to induce fatal anaphylactic shock as well as positive uterine contractions, according to the Schultz-Dale technic in passively sensitized guinea-pigs. Similar results have been reported by Lancefield¹⁶ working with streptococcal carbohydrate substance in guinea-pigs passively sensitized with antistreptococcal serum.

12 Francis, T, and Tillet W J. J Exper Med **52** 561, 1930

13 Avery, O T, and Tillet, W J. J Exper Med **49** 251, 1929

14 Tomcsik K. Proc Soc Exper Biol & Med **24** 379, 1927

15 Tomcsik, K and Kurotchkin, T K. J Exper Med **47** 379, 1928

16 Lancefield R C. J Exper Med **47** 379, 1928

In the field of infection with hemolytic streptococci, bacterial allergy is found in certain phases of scarlet fever and erysipelas. This has been shown by the work of Dochez and Stevens,¹¹ Birkhaug,¹⁷ Zinsser and Ginnell,¹⁰ Mackie and McLachlin¹⁸ and Kirchner¹⁹. In these studies, although the primary inoculation was frequently made with cultures of the respective streptococci, the test substance was a broth filtrate or some bacterial fraction.

Experiments with various nonhemolytic streptococci have been carried out by Derick, Hitchcock and Swift²⁰ in connection with their studies in rheumatic fever which led them to the conclusion that focal infection resulting from inoculations with nonhemolytic streptococci may be followed by a state of hypersensitiveness. This is evidenced by "increased skin reactivity to reinoculation with small doses of streptococci, by marked reactivity of the scarified cornea to installation of streptococci into the conjunctival sac, and by the death of many of the animals following intravenous inoculations with cultures in amounts well tolerated by normal animals."

Finally, the stimulating investigations of Zinsser²¹ on tuberculin hypersensitiveness, which may give a clue to the elucidation of the Poncet type of tuberculous arthritis, have recently been further elaborated by Lewis and Seibert²². These workers have been able to show that proteins isolated from filtrates of acid-fast bacterial cultures on synthetic mediums are actively anaphylactogenic. By the use of the anaphylactic reaction they were also able to establish a definite antigenic relationship between the three types of tubercle bacilli proteins, and to sensitize passively normal guinea-pigs with precipitating serums from guinea-pigs immunized with tuberculin protein.

From this brief summary of recent work on bacterial allergy, it is obvious that evidence is rapidly accumulating to the effect that the allergic state is part of the immunologic mechanism accompanying infection. Before antibodies have been accumulated to any extent in the circulation, the phenomenon is mainly cellular, the first stage expresses itself in an extraordinary irritability of the cell in contact with the antigen. We may say with Zinsser, that "in bacterial allergy we are dealing with sensitization of the body by autolytically liberated

17 Birkhaug, K. E. *J. Infect. Dis.* **40** 549, 1927.

18 Mackie, T. J., and McLachlin, D. G. *J. Brit. J. Exper. Path.* **8** 129, 1927.

19 Kirchner, O. T. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55** 157, 1928.

20 Derick, C. L., Hitchcock, C. H., and Swift, H. F. *Canad. M. A. J.* **20** 349 (April) 1929.

21 Zinsser, H. *J. Exper. Med.* **34** 495, 1921.

22 Lewis, J. H., and Seibert, F. B. *J. Immunol.* **20** 201, 1931.

antigenic substances, which are absorbed from any focus in which bacteria reacted to inflammatory tissues, and as a result of which the body is rendered subsequently sensitive to contact with the same autolytic products, whether they are liberated and absorbed from a chronically existent focus, or from an identical infection subsequently acquired "

In the clinic, interpretation of bacterial allergy is much more difficult. The complex reactions accompanying immunologic processes in the human being are as yet not sufficiently elucidated. Positive skin tests with bacteria or their products do not always establish an etiologic relationship between the organism and the disease under investigation. The reason may perhaps be found in the following facts: 1. Proper antigenic fractions of the incriminating bacteria are not yet available. 2. There may be a relationship between protein fractions of certain bacteria and heterologous organisms that may give rise to confusing reactions. 3. Invasion with living bacteria may so alter the tissues that secondary antigens may develop and be responsible for allergic manifestations. 4. The occurrence of minor secondary bacterial infections in the respiratory passages or the continuous focal presence of certain ubiquitous organisms in the hosts may be responsible for positive reactions on intradermal injection, so that reactions with so-called specific antigens may be obtained in normal persons and be of no special significance.

In view of such difficulties, conclusions as to the nature of this syndrome must be based on a clinical interpretation of symptoms in the light of established experimental and empiric data. The evidence at hand that leads us to suspect that the arthritis may be of the same nature as the asthma rather than coincidental is therefore partly circumstantial and partly factual. It is founded (1) on analogies of essentially atopic syndromes following the injection of soluble foreign proteins, such as horse serum, etc., in which asthma, arthritis and urticaria may occur, (2) on the fact that infectious asthma due to allergy to bacteria, which is admittedly an accepted clinical entity, may be associated with similar symptoms of arthritis, the allergic nature of this condition is further supported by the observations of Zinsser²³ to the effect that "experimentally, in bacterial allergy, it appears that sensitiveness of joints can be demonstrated as to some extent parallel to general sensitiveness", (3) on the findings that the same foci remote from the joints were responsible for the asthma as well as for the arthritic symptoms, this is in line with the work of Swift, Hitchcock and Derick which indicated

²³ Zinsser, H. The Bacteriology of Rheumatic Fever and the Allergic Hypothesis, *Arch Int Med* 42:301 (Aug) 1928, *Bull New York Acad Med* 4:351, 1928.

that focal infection gives rise to a state of hypersensitiveness, (4) on the observations that none of the patients showed toxic manifestations due to the chronic foci, they were ambulatory, and their temperatures rarely exceeded 99 F, and (5) on the marked relief from the asthmatic attacks and the complete disappearance of arthritis following the elimination of the responsible foci of infection in eight of the nine cases.

As a consequence of these findings it can be stated that certain persons may develop sensitiveness to bacterial infection, the effects of which may be manifested in one or more particular distant sites, the respiratory tract or the joints. The clinical manifestations may be asthma or recurrent nasopharyngeal symptoms, such as vasomotor rhinitis or arthritis. The presence of two "shock organs" in the sense of Coca in the same person may induce involvement in both. Atopic sensitiveness may coexist, and when latent, may be brought to the fore by an acute bacterial infection, thus, it may be primary or secondary. In our experience we have frequently noted that an infection in the upper part of the respiratory tract may evoke latent atopic hypersensitiveness.

SUMMARY

In a study of bronchial asthma due to hypersensitiveness to infection, nine cases were observed in which attacks of arthritis developed. The arthritis was migratory, affecting various small and large joints, and was accompanied by redness, swelling and pain on motion, but practically no fever. The duration of arthritis varied from two to four years, whereas that of asthma was from six to fifty years.

In five of the patients, foci of infection in sinuses and lungs constituted the only etiologic factors of the asthma and joint manifestations. In four, besides infection there was a coexistent atopic hypersensitiveness to substances such as ragweed, goose feathers, etc. Simple elimination of these atopens had no influence on either the asthma or the arthritis. Evacuation of pus from antrums, treatment of ethmoids and the consequent recession of the pulmonary focus caused complete subsidence of the arthritis in eight of the nine cases, while the asthmatic seizures diminished in frequency and severity in each instance.

A consideration of recent accumulating evidence of bacterial allergy and its arthritis, tuberculosis, etc., leads us to the conclusion that the allergic state is part of the immunologic mechanism accompanying infection.

In asthma induced by a chronic focus of infection, bacterial allergy is an admittedly accepted mechanism. Coexistent arthritis due to the same focus is in all probability an expression of a similar reaction in

allergic persons in whom the lungs are the primary and the joints the secondary shock tissues

In the present state of knowledge direct proof of bacterial allergy by means of skin tests is difficult to obtain. Interpretation of the nature of the asthma-arthritis syndrome in our patients on the grounds of allergy to bacteria is based, therefore, on known accepted experimental and clinical facts as well as on analogies to similar clinical pictures in the domain of protein hypersensitiveness, such as serum sickness etc.

Correspondence

"EXPERIMENTAL AGRANULOCYTOSIS"

To the Editor —In the January 1932, issue of the ARCHIVES OF INTERNAL MEDICINE is an article entitled "Experimental Agranulocytosis," by B M Fried and William Dameshek

This article implies by title and indicates to the casual reader that the disease, agranulocytosis has been produced by the intravenous injection of *Bacillus pyocyaneus* into rabbits

It is the purpose of this communication to correct any such impression and to call attention to the fact that the results obtained by the authors may be duplicated by a wide variety of substances, including milk, nonspecific proteins dead and living bacteria and various types of inert, finely divided material

In the interpretation of their results, the authors evidently overlooked the fact that a pronounced temporary granulocytopenia results from the intravenous injection of any of the foregoing substances This has long been recognized by research workers and those familiar with hematologic reactions in rabbits Wells (Leucopenia and Leukocytosis in Rabbits, *J Infect Dis* 20 219 1917) injected dead typhoid bacilli, streptococci and staphylococci into rabbits, and concluded "There occurs regularly in the blood, following intravenous injections of foreign proteins a marked reduction of leukocytes, and after several hours, a marked increase of leukocytes" In connection with this quotation, it is significant that Fried and Dameshek killed most of their animals at the end of twenty, thirty, forty and seventy minutes, respectively, at times when the leukopenia was marked Had they been allowed to live, a leukocytosis probably would have developed

Doan and his associates (Doan C A, Zertas, L G, Warren, S and Ames, O A Study of the Mechanism of Nuclemate-Induced Leucopenic and Leucocytic States, with Special Reference to the Relative Roles of Liver, Spleen and Bone Marrow *J Exper Med* 47 403, 1928) showed clearly that in normal rabbits sodium nuclemate induces an immediate, temporary leukopenia due to accumulation of the granulocytes in the spleen, and that this then is followed by leukocytosis, whereas in splenectomized rabbits the leukocytosis is immediate

Since the publication of the work by Fried and Dameshek, I have duplicated all of their reported experiments, using dead typhoid bacilli, and in the larger doses have produced a degree of granulocytopenia, amounting in some instances to complete absence of granular cells That is, if the term agranulocytosis is justified by these authors, it can be produced as well with dead typhoid bacilli or any other dead bacilli as with living *B pyocyaneus*

I wish to differ therefore from the implication by title and text that agranulocytosis was produced by these workers, and to call attention to the fact that they evidently overlooked the well accepted leukopenia that temporarily follows the injection of such substances If desired I will be glad to submit records of animal experiments duplicating their findings with dead typhoid bacilli

Also, in connection with the subject of agranulocytosis I should like to offer a criticism of the proposed term "hypogranulocytosis" used by Conner and his associates in the same issue of the ARCHIVES OF INTERNAL MEDICINE (Conner, H M, Margolis H M Birkeland, I W, and Sharp J E Agranulocytosis and Hypogranulocytosis, *ARCH INT MED* 49 123 [Jan] 1932)

This term, first used by Weiss, should be abandoned because of its obvious incorrectness, meaning "a decreased number of increased granulocytes." A better one, as proposed by Roberts and myself (Roberts, S R, and Kracke, R R Agranulocytosis Its Classification, *Ann Int Med* 5 40, 1931), and consistent with accepted terminology, would be "granulopenia."

ROY R KRACKE, M D, Emory University, Ga

To the Editor—In our studies on experimental agranulocytosis we used *Salmonella supestifer* and not *Bacillus pyocyaneus*, as mentioned by Roy R Kracke. The purpose of our studies was to determine the possible similarity between the *blood picture* as seen in agranulocytosis in man and that found in *one form* of experimental sepsis in rabbits. Our experiments were undertaken in connection with statements to the effect that human agranulocytosis is a disease *sui generis*. The experiments have shown that granulocytopenia may be observed in this form of experimental sepsis. However, no claims were made that the micro-organism used in our experiments was the essential cause of the disease in man or that other bacteria might not produce the same disease in the rabbit.

Simultaneously with our paper in the ARCHIVES, there appeared an article by Roy R Kracke, bearing the identical title that ours did "The Experimental Production of Agranulocytosis" (*Am J Clin Path* 2 11 [Jan] 1932). It is interesting that in this article, to which there is no reference in his letter, Kracke is emphatic in stating that "subcutaneous injections of benzene and olive oil resulted in the development of clinical agranulocytosis in rabbits."

We are aware, as is Kracke, that a pronounced temporary granulocytopenia may be induced in the rabbit by hematogenous injection of a number of substances and of various bacilli. Thus, in quoting unpublished data obtained by us on the peripheral blood picture of rabbits infected with tubercle bacilli, one of us (Dr Fried) stated (*Arch Path* 12 689 [Nov] 1931) that "studies on the peripheral blood of rabbits infected with tubercle bacilli reveal that the infection is followed by an almost instantaneous leukopenia."

Those who have read our paper in the ARCHIVES have noticed that only a small group of our animals were killed shortly after injection of bacteria in order to study the response of their bone marrow. The majority of rabbits, of which only a few illustrative protocols were given, lived for several days.

Kracke states that he was able to induce agranulocytosis in rabbits with dead typhoid bacilli, also quoting Wells and Doan who produced temporary pronounced granulocytopenia with staphylococci, streptococci and other organisms and substances. It is thus of interest that on page 13 of his article, to which we have referred, the following statement is made "I have injected various organisms isolated from the blood-stream of patients with the disease (agranulocytosis) and in each instance have failed to depress the leukocyte count."

We too would not object to replacement of the term agranulocytosis by that of "granulocytopenia" (and not granulopenia, as suggested by Kracke) or of "malignant neutropenia," as suggested by V Schilling and used recently by Dameshek and Ingall (*Am J M Sc* 181 502 [April] 1931) in a clinical report of this condition.

B M FRIED, M D, and

WILLIAM DAMESHEK, M D, Boston

Book Reviews

Cancer and Race A Study of the Incidence of Cancer Among Jews By Maurice Sorsby With a preface by Lt Col F E Fremantle Price, \$3 Pp 120 New York William Wood and Company, 1931

This is a distinct contribution to the literature on cancer, it is of far greater value than many statistical studies published in the past, because the author recognizes the limitations of the validity of his statistical material and refrains from making unjustifiable deductions therefrom. The theme is set forth in a quotation from Roger Williams' book on the "Natural History of Cancer" "The Jewish race being widely scattered throughout the world and the conditions of existence of its various communities being accordingly diverse, is admirably circumstanced for illustrating the comparative importance of race factors *versus* conditions of existence, in determining the incidence of cancer" Furthermore, the Jewish people have in certain cities to a large extent maintained the pure strain of their race. They have kept, to a considerable point of detail, accurate returns over a long range of years. Their ritual laws and habits, moreover, have established definite conditions that differentiate them from the other communities in which they live, and these conditions might be expected to have an influence on the incidence of cancer. This difference and its bearing on the causation of cancer have long been recognized and widely discussed. Under the Jewish Health Organization of Great Britain, Dr Sorsby has carried out a careful and comprehensive investigation of the subject. The results are presented in this book and will be found both interesting and instructive.

A consideration of the mortality from cancer among Jews reveals that the total mortality varies in different Jewish communities, tending to approach that of the non-Jews of that particular city, i e, it follows a geographic rather than a racial distribution. Also, the incidence of cancer per organ in some respects shows striking differences among Jews compared to non-Jews.

The frequently reported observation that cancer of the uterus is relatively infrequent in Jewish women as compared with the Gentile women of the same communities is fully corroborated, and is checked by the demonstration that cancer of the breast does not show any appreciable difference, while cancer of the gastrointestinal tract seems to be more frequent among the Jews. Cancer of the penis is almost never recorded in Jewish patients, and as the same infrequency is observed in the circumcised Mohammedans, this rite is given credit for the immunity rather than any racial difference. Therefore, the low incidence of cancer of the cervix is also thought to depend not on any racial property, but solely on local conditions, probably the sexual hygiene of the Mosaic code, of which Sorsby says, "It is the lasting achievement of the Mosaic code that it has taught Jewish women that vaginal discharges are essentially pathological and avoidable."

While this conclusion may be correct, and racial characters are not responsible for this peculiarity, we have before us the apparently equally marked exemption of Japanese women in respect to cancer of the breast, without the benefit of Mosaic law.

Asthma and Hay-Fever in Theory and Practice By Arthur F Coca Mathew Walzer and August A Thommen Price, \$8.50 Pp 850 Springfield, Ill Charles C Thomas, 1931

This book is written in three parts. Part one consists of 117 pages and was written by Dr Coca. In this section, hypersensitiveness, anaphylaxis and allergy are discussed from a theoretical standpoint. The literature is covered thoroughly.

and an attempt is made to clarify many of the terms that have arisen in these fields. A table is presented giving the essential differences between anaphylaxis atopy, hypersensitiveness of infections, contact dermatitis and serum sickness. These subjects are discussed in great detail from the standpoint of occurrence, age of onset, how established, heredity, mechanism, reaction of the guinea-pig, reaction of the human skin and possibility of desensitization. The last chapter of this section is devoted to the preparation of extracts and solutions for use in testing and treatment in human hypersensitiveness.

Part two is devoted to the consideration of asthma and covers the next 370 pages. Dr. Walzer discusses the early history of the disease, and then at great length writes about the theories of asthma, the pathology, etiology, clinical course and symptomatology, complications and treatment. These subjects are covered admirably and in an interesting manner. The literature has been covered exceptionally well, and, in addition, the author expresses his own views thoroughly. Dr. Thommen assisted Dr. Walzer in writing the chapter on "The Methods of Testing for Hypersensitiveness," and Miss Katherine Bowman assisted in the chapter on "Atopics and Other Excitants." This last chapter is of a great deal of interest because of the detailed discussion of every excitant. References are given for more complete study of each substance.

The third part, devoted to the discussion of hay fever, consists of 300 pages and is written by Dr. Thommen. The history of hay fever is taken up first, and then the essentials of flower structure and the process of pollination are discussed. Before the etiology and mechanism of hay fever are considered, the author describes in the greatest detail all the plants, grasses, trees and weeds that have any bearing on the disease. The practical side of the diagnosis and treatment of hay fever is as well discussed as the theoretical consideration in the earlier chapter. The whole subject is handled in an admirable manner.

The book contains a wealth of information and a bibliography that is hard to surpass. It should be of the utmost value to any student of hay fever and asthma.

Röntgenuntersuchungen am Innenrelief des Verdauungskanals, ein Beitrag zur klinischen Röntgendiagnostik insbesondere von Entzündung, Geschwür und Krebs. By Prof. Hans Heinrich Berg, Chefarzt der medizinischen Klinik der städtischen Krankenanstalten in Dortmund. Second edition. Price 50 marks. Pp. 248, with 247 illustrations. Leipzig: Georg Thieme, 1931.

The first edition of this work, published in 1930, is now offered in forty-six more pages and with fifty-four more illustrations. The text is amplified, and more attention is paid to technic and sources of error. The most noteworthy additions pertain to the esophagus, diaphragmatic herniations, the stomach on which an operation has been performed and the colon.

For those who are unfamiliar with the first edition, it may be said that the work is one of the choicest contributions to the literature of gastro-enterology. Berg, an old pupil of Forssell's, pioneered in the systematic roentgenologic examination of the digestive tube by the use of sufficiently small amounts of barium to bring out the relief picture of the mucosa. His disciples, notably Gutzeit, Albrecht and Knothe, have done much to further its development.

The book begins with a historical review, which is followed by a detailed discussion of technic and of possible errors. The underlying anatomic and physiologic considerations are well presented. Normal conditions are described and pictured. The pathologic changes are critically discussed and beautifully illustrated with excellent reproductions of films and frequently with photographs of the anatomic specimens. It is a pleasure to recommend this classic most highly to all students of roentgenology and gastro-enterology.

PAIN IN MUSCULAR ISCHEMIA

ITS RELATION TO ANGINAL PAIN

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The term *angina pectoris* is usually and properly used to indicate the disease as it was described by Heberden and his contemporaries. It is not with the general pathology of this disease that I propose to deal, but rather with one problem related to it, namely, the origin of the pain that characterizes the attacks that render this malady so distressing. There is perhaps no symptom familiar to clinicians that has given rise to more speculation than that of anginal pain. The theories that have been put forward to explain it are too numerous to pass even in review, such a review will not be attempted, but the problem will be approached from a special angle that is relevant to the new observations to be described.

The idea that *angina pectoris* can arise out of a morbid change in the coronary vessels came, as Parry¹ has said, from Edward Jenner. His idea was being fostered a hundred and fifty years ago in the small Gloucestershire Medical Society of which Jenner, Parry and Paytherus were members. From his letter to Heberden² it may be inferred, perhaps, that Jenner believed these vessels to be unable to perform their functions, and that this failure of function is responsible for the painful spasms. It is, however, in the writings of the distinguished Welsh physician Parry that the baneful effects of cardiac ischemia are first expressed with clarity. His words constitute so important a step in the history of this subject that they are here quoted.

The rigidity of the coronary arteries may act, proportionably to the extent of the ossification, as a mechanical impediment to the free motion of the heart, and though a quantity of blood may circulate through these arteries, sufficient to nourish the heart, as appears, in some instances, from the size and firmness of that organ,

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From the Department of Clinical Research, University College Hospital Medical School.

The Frank Billings Lecture delivered in Chicago, Oct. 31, 1931. This material was also used in the St. Cyres lecture, London, May 14, 1931.

1 Parry, C. H. *An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris*, London, Cadell & Davis, 1799, pp. 3, 113 and 114.

2 Baron, J. *Life of Edward Jenner*, London, H. Colburn, 1827, p. 39.

yet there may probably be less than what is requisite for ready and vigorous action. Hence, though a heart so diseased may be fit for the purposes of common circulation, during a state of bodily and mental tranquillity, and of health otherwise good, yet when any unusual exertion is required, its powers may fail, under the new and extraordinary demand. Accordingly we find, that paroxysms of the Syncope Anginosa are readily excited by those passions, the tendency of which is to stimulate the heart to excessive contraction¹

This clear and important statement is one of Parry's chief contributions to the knowledge of angina pectoris. It is not, however, the statement for which he is usually remembered. Parry was convinced of the essential part played by syncope in the disease, and to him the syncope of angina pectoris was equivalent to failure in the strength of the heart beat and led to cessation of its motion. Parry overemphasized the frequency and therefore the importance of syncope. Although in his recapitulation he said that angina pectoris "is a case of syncope, preceded by a notable anxiety or pain in the region of the heart," thus acknowledging the pain as of early occurrence in the attack, subsequently he described pain extending from the breast to the left arm as an "accidental symptom" and as one occurring in other states. Thus, while Parry brilliantly conceives the heart to be crippled in its reserve by the incapacity of its nutrient vessels and thus explains the spasmodic nature of the symptoms, yet he keeps pain in the background and brings weakness of the heart beat into the foreground. The impressive writings of Parry were well known to Burns,³ and the leading ideas in the following extract and in other relevant passages of Burns' book coincide with and are clearly derived from those of Parry. Thus Burns said

In health, when we excite the muscular system to more energetic action than usual, we increase the circulation in every part, so that to support this increased action, the heart and every other part has its power augmented. It, however, we call into vigorous action, a limb, round which, we have with a moderate degree of tightness applied a ligature, we find that then the member can only support its action for a very short time, for now its supply of energy and its expenditure, do not balance each other, consequently, it soon, from a deficiency of nervous influence and arterial blood, fails and sinks into a state of quiescence. A heart, the coronary vessels of which are cartilaginous or ossified, is in nearly a similar condition, it can, like the limb, be girt with a moderately tight ligature, discharge its functions so long as its action is moderate and equal.

Burns here compares the heart and the limb to which the blood flow is impeded, but in doing so he followed Parry's lead and wrote, not of pain but of an organ failing and sinking into a state of quiescence, as did Kreyssig⁴ a few years afterward and Benjamin Brodie⁵ forty-

3 Burns A. Observations on Some of the Most Frequent and Important Diseases of the Heart, etc., Edinburgh, Bryce & Company, 1809, p. 138

4 Kreyssig Die Krankheiten des Herzens 1816, pt 2 p. 512

5 Brodie, B. C. Lectures Illustrative of Various Subjects in Pathology and Surgery, London, Longman [and others], 1846, p. 360

seven years after Parry,⁶ in making similar comparisons. As will be seen a little later, when a voluntary muscle is deprived of circulation and is vigorously worked, pain and not weakness brings its movements to an end. If one holds Parry's view that, in anginal attacks, weakness of beat and syncope are common manifestations, then Burns' analogy would possess more point, and it would be more important if one were considering only prolonged anginal attacks threatening to deprive or actually depriving the subject of life. Burns' analogy has not the same historical significance in relation to the production of pain, which is here under particular consideration. It is not until one considers the work of Potain⁷ (1866), who had behind him the full accounts of his countrymen on "intermittent claudication," that one finds pain arising from heart and from the limb clearly compared. Thus, the important idea of cardiac pain arising out of an ischemic condition⁸ of the working organ has grown slowly but steadily toward clarity, it has not failed to find notable support⁹ (as by Balfour,¹⁰ Huchard¹¹ and Mackenzie¹²).

If one is to grasp fully the possible significances of comparing pain arising in a working limb and in the heart, each inadequately supplied by blood, and if one is to ascertain if the comparison leads one ultimately beyond a simple analogy to find a fundamental pain factor common to the two instances, it will be necessary to analyze the mechanism of such pain more closely and to obtain clearer ideas of the factors influencing it than has been done hitherto. The idea is too important to be left at the stage of hypothesis.

I shall begin, therefore, by considering at some length how in the case of the limb such pain arises.

6 Brodie however was the first to draw the analogy between intermittent claudication and angina.

7 Potain, in *Dictionnaire encyclopedique des sciences medicales*, Paris, V Masson et fils, 1866, vol 4, p 346.

8 While it will be agreed that pain is an almost constant and a chief feature of the anginal seizure, the idea that ischemia of the heart is responsible for no more than pain is one that could scarcely be allowed. The text emphasizes the symptom pain because pain is the symptom the mechanism of which is under consideration.

9 A clear account has recently been published by C. S. Keefer and W. H. Resnik (*Angina Pectoris. A Syndrome Caused by Anoxemia of the Myocardium*, *Arch. Int. Med.* 41: 769 [June] 1928).

10 Balfour, G. W. *The Senile Heart, Its Symptoms, Sequelae, and Treatment*, London, A. & C. Black, 1896.

11 Huchard, Henri. *Traite clinique des maladies du coeur et des vaisseaux*, Paris, O. Doin, 1899, vol 2, p 151.

12 Mackenzie, James. *Angina Pectoris*, London, Oxford University Press, 1923, p 36.

THE ORIGIN OF PAIN IN ISCHEMIA OF THE LIMB

Two main views have been held in attempting to account for the pain in ischemia of the working limb. One of these, which is still chiefly favored on the European continent, is that pain comes from arterial spasm.¹³ This view may be dealt with briefly and excluded, since Pickering, Rothschild and I¹⁴ have found it easy to show that when the muscles of the forearm are exercised while deprived of blood supply, the vessels to the corresponding part of the limb actually lose their tone. If the circulation to an arm is arrested and the muscles of the forearm are exercised vigorously until pain is intense, plethysmographic records demonstrate that, immediately after the circulation is released and exercise is stopped and while pain still continues, the forearm is flooded with blood owing to the vessels being at the time widely open.

The second view, which has been more favored in England, is that the pain is of muscular origin. Charcot¹⁵ was first responsible for this view, though he had the idea that the muscle enters on a condition of cramp, which he likened to "cadaveric rigidity," an idea that, as will be seen later, is untenable. There has been, in fact, little or no observational work that throws light on the mechanism of the pain under consideration and recognizing this Dr. Pickering, Dr. Rothschild and I undertook a series of new observations,¹⁴ which will now be discussed.¹⁶

The exercise used has been a simple gripping movement. The contractions are almost maximal, at the rate of one a second. The circulation is arrested during the exercise by means of a sphygmomanometer cuff, which is distended to a high pressure on the upper arm. In an observation of this kind, pain begins from about twenty-five to forty-five seconds (or the same number of contractions) after the beginning of exercise, it develops progressively, increasing in intensity and rendering a continuation of exercise still vigorously pursued, very disagreeable or intolerable at about the seventieth second. It is to be emphasized that if the exercise is done under suitably controlled conditions, the time

13 The corresponding idea has been held also in the case of the heart, namely, that anginal pain arises directly out of spasm of the coronary arteries in cardiac ischemia (see Gallavardin, L. *Les angines de poitrine*, Paris: Masson & Cie, 1925, p. 126).

14 Lewis, Thomas, Pickering, G. W., and Rothschild, P. *Heart* 15: 359, 1931.

15 Charcot. *Progres med* 6: 99, 1887.

16 The fact that pain occurs in muscles exercised in the absence of a blood supply has long been known. It was an observation frequently referred to by Mackenzie. Zak studied the phenomenon (in 1921), but, as we think, misinterpreted it. In our original paper we overlooked MacWilliam and Webster's article (*Brit M J* 1: 51, 1923); this paper deals in the main with the relation of pain and fatigue, but here and there covers ground similar to our own.

at which pain develops to the point that for convenience is termed intolerable can be estimated by the subject within narrow limits of error, and the time proves to be remarkably constant in repeated tests by one subject and in different tests by different subjects. The pain has a peculiar and characteristic aching quality. Although it may be described as rather diffuse, yet it is felt maximally in the region of the muscles most exercised. Thus the situation in which it appears can readily be altered by throwing the burden of exercise mainly on this or on that group of muscles. An important point is that the pain is continuous, it does not increase appreciably with the contraction of the muscle, and it does not subside with the relaxation. It is a smooth pain, gradually but constantly growing in intensity while exercise lasts. Thus, it is shown to be independent of the tension developed during the contraction of the muscle.

The pain is not the result of cramp, for in none of our observations has there been any sign of tonic contraction, relaxation being complete between each movement. We are not prepared to say that cramp never occurs as an accompaniment, but it is quite clear that cramp is unessential to the production of the muscular pain described¹⁷. Tenderness is developed in the region where pain has been felt, namely, in the group of muscles most exercised, and may last for a long time after the pain has disappeared.

We have shown that the pain is not the direct result of a lack of oxygen. Of these observations, the most conclusive is perhaps the following. The forearm, deprived of its blood supply, is exercised in the usual way, and the exercise is continued until pain begins, this time is noted. After a period of rest, the exercise is repeated in exactly the same way, but it is stopped a few seconds before pain is anticipated. Although the arterial occlusion is prolonged for a further period of five minutes, no pain develops. Now if pain is to be attributed to lack of oxygen, it is clear that at the instant exercise ends the amount of oxygen in the tissues must have declined almost to the necessary level for the production of pain. Yet, although during the immediately succeeding period oxygen will still be used up rapidly owing to the oxygen debt that has been established in the muscle, no pain develops. Thus it is impossible to accept the view that in this experiment pain fails to develop simply because the oxygen deficiency is not carried far enough. The relationship is not to the lack of oxygen but to the muscular exercise, and the time at which pain appears is governed by the amount of exercise taken. If the rhythm of muscular contraction remains con-

¹⁷ P. M. Latham (*Lectures on Subjects Connected with Clinical Medicine*, etc., London, Longman [and others], 1846, vol. 2, chap. 37) believed that cramp of the heart muscle causes angina, but this idea now finds little or no support.

stant, then the pain begins earliest in those exercises in which the tension developed at each contraction is greatest. On the other hand, if the tension developed is kept constant, then the time at which pain develops is controlled by the rhythm of the contractions, the faster the rhythm, the quicker the pain will come. Usually the pain comes after a given number of contractions developing a given tension, whether the rhythm of contraction is slow or fast. From these experiments and from supporting evidence presently to be given, it is concluded that when muscles deprived of blood supply are exercised, the pain that develops is due to a stimulus arising directly or indirectly out of the contraction process.

A most important clue to the nature of the pain mechanism is provided by the following very simple observations. The circulation to the arm is arrested, and exercise is undertaken until pain develops to a given degree. If the exercise is now stopped but the circulatory arrest is continued, the pain does not subside but continues. It continues at the intensity that has been developed by the time exercise ends, and it is maintained at this intensity so long as the circulation remains arrested. But if the circulation is released at any time subsequently, the pain disappears completely within from two to four seconds. This observation has led us to the view that the pain is determined by some chemical or physicochemical agency within the mass of muscle, for the factor underlying pain continues unchanged until the circulation is restored, when it is promptly removed.

It will perhaps facilitate description if I anticipate and state that we believe the stimulus causing pain to have its seat in the tissue spaces; the reasons for this belief will appear later. When a muscle contracts changes such as the release of metabolites occur within its fibers, one obvious possibility is that these metabolites diffuse out and comprise the stimulating agent in the spaces, however, we wish to avoid committing ourselves to a conclusion in this form, since it is also possible that changes within the fiber may induce secondary and distinct changes within the spaces. So it becomes necessary to keep relevant changes within and without the fiber as distinct ideas, we do so by naming the latter the pain factor or "factor P," because it constitutes the immediate stimulus to pain.

When a muscle is exercised under ischemic conditions, factor P, once formed remains unchanged. Moreover, it is cumulative, increasing in amount with each muscular contraction, it rises first to a level adequate to bring pain and then to higher levels, associated with increasing pain. Because it is stable during circulatory arrest it maintains the pain between muscular contractions and after exercise has ceased.

Consider next the interpretation of what happens when the circulation to the muscles is released. In the usual exercise the time taken

for pain to develop from its beginning to its intolerable point is about thirty-five seconds. The amount of factor P responsible for this development of pain is dispersed in from two to four seconds of the restoration of the blood flow to the muscles. This rapid recovery is, in our view, a recovery confined to the tissue spaces. Recovery of the underlying process in the fiber itself takes much longer. If, a little time after release, the circulation is rearrested and the exercise is repeated, the time taken for pain to reappear is shorter than in the original exercise, and the amount of shortening is related to the shortness of the period of release intervening. Actually, it is found that this period of release between two exercises must extend to ten minutes if the times for the development of pain in the first and second exercise are to be made to correspond. This interval of ten minutes is the approximate time taken for the recovery of the muscle fiber, so far as those processes ultimately underlying the production of pain are concerned.

If the exercise is begun and the circulation is arrested some time later, the exercise being continued, the preliminary period of exercise with free circulation is unaccompanied by pain, but it shortens the time taken for pain to develop in the subsequent period of exercise under ischemic conditions. Observations of this kind indicate that during muscular exercise with the circulation free the change within the muscle fibers that ultimately underlies pain occurs, but pain does not develop, since factor P cannot accumulate in the tissue spaces while these are under the influence of a free stream of blood. Confirmation of this view is found in experiments of the following type. If the exercise is undertaken with the circulation free for a period of two minutes and if the blood flow is then arrested and the exercise stopped simultaneously, there is no pain, but pain develops after a latent period of about from twenty to thirty seconds and may become severe within one minute. In this instance, the processes underlying the production of pain occur during the exercise, but factor P cannot rise to a corresponding level in the tissue spaces until some time after the circulation ceases.

When pain has developed in the usual exercise under ischemic conditions and has been abolished by release of the vessels, the pain returns after a latent period if the blood supply is rearrested. The latent period is shorter and the intensity of the pain developed is greater if the period of release is short. In this instance, factor P is reduced or abolished in the tissue spaces during release and accumulates on rearrest, the level to which it reaccumulates naturally depends on the amount by which the muscle fiber recovers during the release.

These are the main evidences for the conclusion already formulated that factor P acts in the tissue spaces, but is dependent on processes occurring within the muscle fiber as a result of its contraction. When the blood flow is arrested, the process in the muscle and the accumulation

of factor P in the tissue spaces occur *pain passu*, with the circulation free the same process occurs in the muscle fiber, but the condition of the tissue spaces is kept relatively unchanged

The observations here briefly recorded¹⁸ are relevant to the main thesis of this article. They afford, for the first time, evidence for the belief that in ischemia pain arises from a working muscle, and that the stimulus is derived from physiologic processes in the muscle fiber. Further, if the characteristics of anginal pain and the various circumstances in which it arises and is influenced are closely considered in the light of these observations on somatic muscle, much that was previously obscure becomes plain to the understanding.

ANGINAL PAIN

Anginal pain is believed to result from relative ischemia of the muscle. This view does not ascribe it to a simple mechanical cause, but recognizes that it may be provoked in distinct ways. Thus, it may be provoked if the blood supply to the muscle becomes diminished, while the work done remains constant, or it may be provoked if the blood supply fails to increase adequately to the needs of a muscle that is called on to increase its work.

Coronary Occlusion, Diminished Blood Supply—One of the most powerful arguments for the theory that anginal pain is caused by muscular ischemia is the symptomatology of acute coronary occlusion.

It is established beyond any reasonable doubt by clinical observation that pain is produced by occlusion of the coronary vessels, and that this pain is indistinguishable from that of angina pectoris in situation, radiation and character. If, as would appear, the pain of coronary occlusion is more frequently epigastric than is the other, the fact is still unexplained, however, coronary pain often starts in other places, in the region of the upper part of the sternum, over the precordium or even in the left arm as does the pain of angina pectoris. Starting usually in the chest it radiates to the left arm, both arms, the neck, jaw, abdomen or scapula, as does spasmodic anginal pain. The unfortunate sufferers in the two groups use a precisely similar series of descriptive terms in trying to make known the character of the pain. In both groups a sense of weight or constriction as an integral part or accompaniment is referred to frequently, as is also alarm that death is coming. Those who are interested may profitably study the fine series of case notes published with autopsies by Levine.¹⁹ In clinical cases, the

18 A full statement of the results will be found in a contemporary publication (footnote 14).

19 Levine S. A. *Coronary Thrombosis: Its Various Clinical Features*, Baltimore: Williams & Wilkins Company, 1929.

occlusion is usually by thrombosis (sometimes by embolism), forms of obstruction that are open to the very least objection as uncomplicated instances of arrested blood flow. The patients afford a much safer source of information regarding the symptom pain than do experiments on animals in which there is deliberate interference with the coronary vessels. Percy, Priest and Van Allen²⁰ and Sutton and Lueth²¹ repeatedly observed evidences of pain, referred seemingly to the left foreleg, after ligation of a coronary vessel or its branch in dogs. These observations corroborate what has been established clinically. The chief value of Sutton and Lueth's work lies in their failure to awaken painful impulses from the heart in any other way than that of interrupting the coronary stream.

Since severe pain is known to occur when the coronary artery is occluded, whether by ligation or by internal clot, it is difficult to refrain from concluding that it originates from the heart, as it does from the limb, through muscular ischemia, and since in the latter case it is concluded that the underlying process occurs in the muscle fiber and is due to muscular contraction, the stimulus acting actually in the tissue space, it may be assumed that similar processes underlie the pain of coronary occlusion. All our evidence is quite compatible with this view. The pain of coronary occlusion is continuous, it does not come and go with the heart beat. It begins as a slight pain and grows steadily, and often rapidly, in intensity. In these features it is like the pain derived from somatic muscle in similar circumstances. In its continuity this pain differs from that produced by overloaded involuntary muscle, as, for example, the bowel, each separate contraction of which induces a simultaneous spasm of colic. Our theory explains this continuity. It is not tension developed in the heart that brings pain, but a chemical or physicochemical stimulation of its afferent nerves. This stimulus will begin to form in the tissue spaces from the instant of occlusion, and the pain will come the sooner in the case of the heart because the muscle is in continuous work at the moment of arrest. Sutton and Lueth called attention to the pain coming immediately or almost immediately, a point of much interest, if the circulation is arrested to somatic muscle already working continuously, the pain may begin within eight seconds, when the rhythm is sixty contractions a minute; it occurs more quickly if the rhythm of contraction is quickened. The almost instant appearance of pain in coronary occlusion is not inconsistent with the view put forward. The prompt relief when the ligation is released is entirely consistent with this view.

20 Percy, J. F., Priest, W. S. and Van Allen, C. M. *Am Heart J* 4: 390, 1929.

21 Sutton, D. C. and Lueth, H. C. *Pain*, *Arch Int Med* 45: 827 (June) 1930.

In thrombotic occlusion the pain lasts for hours or even days, and in this it differs chiefly from the pain in attacks of angina pectoris. According to our theory, it must be long lasting. When a coronary vessel is plugged, a corresponding area of muscle loses its blood supply, if in an experiment one watches the cardiac wall, the affected area becomes darker, gradually it loses its power to contract and balloons outward at each systole of the ventricle. The loss of function happens over a period of fifteen minutes or more. Long before this degree of weakness develops, according to experiences with somatic muscle, factor P, the pain stimulus, will be accumulated sufficiently to give intense pain. Once accumulated it will continue there, whether the muscle beats or not, and will give rise to pain as long as it can affect living sensory nerve endings. Sooner or later the nerves in the fully affected region will become paralyzed, and painful impulses will cease to ascend these, however, it is obvious that the nerves on the margins of the bloodless zone may be affected for much longer times.

Long-lasting pain is explained without difficulty. The duration will vary according to circumstance, one factor governing variation will be the rate at which the affected nerves die. Another factor that will influence the pain will be restoration of the blood flow, for the whole area of muscle that becomes ballooned does not necessarily die, a part or even the whole is often found in experiment to be restored to action by a return of blood through anastomotic channels. It suffices for the moment to note that conspicuous variations in the duration of pain, and even of its intensity from hour to hour, are possible theoretically, they are actually experienced.

Spasmodic Anginal Pain, Blood Supply Inadequate for Work Done
—No theory explaining the pain can stand that will not account for its appearance in attacks, and in angina pectoris the relation of such attacks to exercise and to emotion has been recognized from the earliest days of its description. It was indeed the spasmodic nature of the malady that led Parry to state his theory of relative ischemia, for this theory afforded a ready explanation. It was this spasmodic nature that led to the comparison with intermittent claudication, for in both instances it is to be supposed that the vessels can supply enough blood during rest but not during work.

It is instructive at this point to contrast two views. The belief²² that attacks of anginal pain can result from increased strain on a structure such as the aorta is distinctly equivalent to the belief that it is the result of raised pressure for that alone can throw the walls of the corresponding cavity temporarily into increased tension. Under

²² Allbutt, T. C. Diseases of the Arteries Including Angina Pectoris, New York, The Macmillan Company, 1915.

the theory of ischemia and as exemplified by our investigations of somatic muscle, if the blood supply remains constant, the attacks of pain will result from the increased expenditure of energy, this expenditure will increase when the tension (blood pressure) is raised, it will also increase if the rate of beating is increased, the tension remaining constant. In this connection, it is most interesting to note that cases have been recorded in which characteristic anginal pain has occurred constantly with paroxysms of tachycardia, for such paroxysms, while failing to raise blood pressure, greatly increase the energy expended by the cardiac muscle. The hypothesis of strain cannot account for pain in these circumstances, that of relative ischemia does.

To the belief that angina is the result of mechanical strain, the similar appearance of the anginal attack at given levels of blood pressure is essential, to the theory of muscular ischemia, it is unessential. It will be evident how important is full knowledge of the changes of blood pressure and pulse rate in anginal seizures, yet, while much has been written on what is assumed to occur, little observational work has been undertaken to ascertain whether the facts do or do not fit with theory. It is easy to assume, because the blood pressure and pulse rate are known to be raised by exercise under normal conditions, that exercise always raises them when it provokes anginal pain. I do not doubt that such changes will be found, will prove adequate and will thus come more fully to justify explanations of anginal pain that are based on them, but the assumption remains, and is dangerous, until the pressures and rates have been read. When, as is so common in patients with angina, walking rather briskly on level ground induces the early tightness across the front of the chest, is one right in believing that there is, in fact, a rise in the expenditure of energy of the heart adequate to produce pain, and that an equal rise, however provoked, will always produce pain? The answer will come from appropriate observation and experiment.

There is a feature manifested by anginal pain provoked by effort that is not unusual, which was first described in that historic and remarkable letter of an unknown gentleman to Heberden²³. He wrote "I have frequently, when in company, borne the pain, and continued my pace without indulging it, at which times it has lasted from 5 to perhaps 10 minutes, and then gone off." That is a phenomenon difficult to explain on a simple basis of pressures and rates, but is easy to understand if it is believed that the coronary circulation accommodates itself gradually to the condition of exercise. It is, of course premature to speculate in this way, it would be more satisfactory if one waited

²³ Medical Transactions published by the College of Physicians in London, 1875, vol 3, p 3

What actually happens to the pressure over the time pain is disappearing under exercise can be, but has not yet been, ascertained. If I express the belief that no appreciable change will be found in it, I am anticipating what should first be demonstrated one way or another. My purpose here is not to use assumptions as arguments, but merely to point to obvious gaps in the knowledge in relation to anginal pain produced by effort.

I shall now consider another type of angina namely, a type that occurs in patients at rest, and here I have definite and relevant information to offer.

From personal observations and by searching past records, I have been able to bring together a group of cases of a given type. A general description of this type, already exemplified elsewhere,²⁴ will suffice.

The Syndrome—The syndrome may be described on the basis of my own series of cases and the single cases of Brunton,²⁵ Hunter,²⁶ Powell²⁷ and Mackenzie,²⁸ all of which are grouped together. Repeated and close observations have been made on patients of this type during anginal attacks, the pulse rate and blood pressure being studied in particular. The cases almost always occur in male patients who have free aortic regurgitation, though I have met with the characteristic syndrome in one middle-aged man in whom no signs of aortic valvular disease could be found. The patients have grave cases of heart disease are often bedridden and at the most are capable of only slight exercise. They may live precariously for years, sudden death among them is common.

The pain has the usual, though variable characteristics of grave angina pectoris. It is located at first in the front of the chest centrally, over the upper part of the sternum, or less commonly near the left nipple. It is a continuous boring or gripping pain, acquiring in the major attacks an unbearable quality, it spreads characteristically into the arms, especially into the left. It may or may not be associated with a feeling of intense anxiety. In the earlier stages of the malady, the attacks of pain which last from a few minutes to half an hour or more, may be provoked by exercise in which case they bring the patient to a state of immobility. In later stages when little exercise is possible, they occur while the subject is at rest and seem particularly prone to happen in the early hours of the morning waking the patient from sleep. The attacks also occur by day and may be provoked by the

24 Lewis, Thomas. *Heart* 15 305 1931

25 Brunton. *Lancet* 2 97 1867, *Clin Soc Rep* 3 191 1870

26 Hunter. *Brit M J* 2 1128, 1909

27 Powell, in Allbutt C. A. and Rolleston H. D. *A System of Medicine*, New York, The Macmillan Company, 1910, vol 6 p 183 (case 5)

28 Mackenzie, James. *Heart* 2 265, 1910-1911

ingestion of food or by the idea of food. The patients, in relating the symptoms of the attack, frequently speak of strong throbbing of the wall of the chest, rapid and violent beating of the heart and the neck, a feeling of tenseness and a throb invading the head. General pallor is not a feature of the attack, on the contrary, the face may flush, sometimes to a deep suffusion, if pallor comes eventually, it is inconspicuous and confined to the face. A distinctive feature is a change of heart rate and of blood pressure, both lifting to high points. Rapid breathing in the attack is the rule, and is probably a special feature, sweating is the rule, but is not distinctive. It is well known that in many instances of repeated anginal seizure, amyl nitrite fails to bring relief, in the type of case described, the remedy is efficacious, rarely failing to stop the pain. In this connection, it is of particular interest to note that the first case described to illustrate the beneficial action of amyl nitrite, the famous case recorded by Brunton, was of this type. I believe the syndrome to be the usual anginal syndrome at rest in cases of free aortic regurgitation.

Numerous observations on the blood pressure, immediately before and during the attacks, show that the disturbance of the vascular system in the attacks is not provoked by pain, since pain definitely succeeds the rise in blood pressure. The more plausible, though converse, idea that in these cases pain is due simply to the imposing of strain of a given quantity, either distending an inelastic aorta or overburdening the working ventricle, likewise fails, for on more than one occasion, after ascertaining the height to which the blood pressure and pulse rate had risen in attacks of pain, equal disturbances of blood pressure and pulse rate have been observed to occur spontaneously, or have been induced by giving exercise, without any trace of pain developing. In other instances, an attack of pain associated with high pressure has subsided, while the blood pressure has remained without appreciable change (or while it has even lifted a little) and the pulse rate has remained as high as before. Putting the matter more generally, it may be stated as a result of direct and careful observation that while attacks are accompanied by a rise of blood pressure and pulse rate, the periods of pain do not correspond with sufficient accuracy to the periods over which pressure and pulse rate equal or surpass what might be regarded as critical levels. Nevertheless, although pain does not provoke the rise of pressure and the high pressure cannot be regarded as the sole determinant of pain, the two phenomena may not be divorced. However, it appears almost necessary to assume that the strict relation between pain and the energy expended is broken by some factor of interference, and the factor in mind is an inconstant state of the coronary vessels. If one accepts the theory of muscular ischemia, then different states of coronary

tone adequately explain discrepancies. If these vessels are involved in the storm and acquire increased tone, then, even if they are not actually constricted they may fail to carry the extra stream of blood that the heart, beating under an unusual burden, requires of them. If pressure and pulse are raised in some other manner, as by exercise, the increased burden may fall on a heart the coronary flow of which is freer, and thus pain may fail to occur. There is no warrant for regarding the coronary circulation as a purely passive system, the flow through which is governed merely by systemic pressure.²⁹

Action of Amyl Nitrite—In considering why amyl nitrite relieves the pain in anginal attacks, its influence on the blood pressure forms a first enquiry. The effect of the drug on the blood pressure during the anginal seizure itself is alone completely relevant and completely safe to use. Few such observations are available from past records. Brunton,²⁵ Hunter,²⁶ Mackenzie²⁸ and Aubertin and Gambillard³⁰ all recorded considerable falls in isolated cases, but these few records by no means fully represent the facts. Among a large series of observations for the investigation of this point, I have certainly seen instances in which the blood pressure has fallen considerably after the inhalation, but almost as frequently, if the blood pressure is taken as soon as the patient has lost his pain, the blood pressure is found to present no material change, and in a few instances has actually been found a little raised. Brunton was led to try amyl nitrite for anginal pain because he knew that bleeding relieved this pain, and he believed this relief to be due to a diminished arterial tension. Amyl nitrite, already known to cause vasodilatation, seemed to him the drug that should act similarly, it was natural that, having found it to give relief, he should refer the effects to a fall of blood pressure. Although his conclusion has retained almost universal assent, it has never received sufficient support from immediately relative observations, and facts conflicting with it have now been brought forward. While it is acknowledged that amyl nitrite may lower vascular tension in the attack—and it is granted that in such instances the fall of pressure is possibly adequate to relieve pain—the point to be impressed is that sometimes the fall is inadequate, and that then another explanation must be sought.

29 In an important paper, Feil and Siegel (*Am J M Sc* **175** 255, 1928) suggested that transient vascular changes occur in the heart muscle in attacks of angina pectoris, on the basis of observed changes in the form of the electrocardiogram during the attacks. Dr Feil has recently shown me curves demonstrating these changes in electrocardiograms taken in a case of aortic disease during angina of the type here considered.

30 Aubertin, C, and Gambillard, M. *Bull et mem Soc med d hop de Paris* **48** 136, 1924.

It seems to have been suggested first by the French clinician Huchard, though on what evidence is unclear, that amyl nitrite may bring relief by opening up the coronary vessels. It has since been shown by experiments on animals that nitrites dilate these vessels.

If one accepts the idea that attacks of anginal pain are brought about by relative ischemia of the muscle, the relief of pain by nitrites may clearly come through a decrease of expenditure of energy, an increase of blood supply or by the joint effects of these two. On the basis of the theory of muscular ischemia, there is no difficulty in understanding why amyl nitrite fails to give relief in the pain of coronary occlusion. Similarly, in angina pectoris there is no difficulty in explaining why amyl nitrite may at times relieve pain without lowering the blood pressure, or why at other times the blood pressure may fall without relief until later. It is also easy to understand why, after the administration of amyl nitrite, the pressure may rise to a high point without causing pain, since the effects of increased coronary flow on the muscle may long outlast the action of the drug. Lastly, it enables one to explain on similar lines why attacks that would otherwise last ten minutes or more are brought to an abrupt and complete end by the inhalation, the direct effects of which are notoriously quite transient.

In this article I have not reexamined the theory of muscular ischemia as a cause of anginal pain exhaustively, but have dealt with those aspects of it that have been given prominence by recent work. This work has brought much support to an old theory and by more sharply defining it has rendered it more tangible and more capable of proof or disproof.

AURICULAR FIBRILLATION

AMBULATORY TREATMENT WITH QUINIDINE

S A WEISMAN, M D

MINNEAPOLIS

In a review of a considerable part of the literature on the use of quinidine sulphate in the treatment for auricular fibrillation, in every instance to my knowledge the patients were hospitalized for treatment. No mention is made of any patient or group of patients who were treated by the ambulatory method. This report deals with twenty-four patients with auricular fibrillation who were treated with quinidine sulphate in the outpatient department of the University of Minnesota.

Since 1918, when Frey¹ introduced quinidine as a therapeutic measure in the treatment for heart disease, much has been written about its efficacy, its toxic effects and the complications resulting from its use. Almost every report in the literature relates instances of the following complications: distressing palpitation, acute heart failure, diarrhea, respiratory or cerebral disturbances and emboli.

There is reason to believe that quinidine has not been given the place it deserves in the treatment for heart disease. Many of the complications that are attributed to quinidine are perhaps due to causes inherent in the patient's condition. The drug is usually blamed immediately when an embolus occurs during treatment with quinidine, especially if the embolus appears after the heart beats become regular, or if the patient dies suddenly during the course of treatment. Death may be due to the drug in some instances, but it is well known that not infrequently accidents occur in fibrillating hearts during treatment with digitalis or without treatment.

Viko, Marvin and White² compiled from the literature a group of 484 cases of auricular fibrillation in which treatment with quinidine was given and compared them with 200 cases of auricular fibrillation at the Massachusetts' General Hospital in which this treatment was not given.

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From the Department of Cardiology, University of Minnesota Medical School

1 Frey W. Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, Berl klin Wchnschr 55 450, 1918

2 Viko, L E, Marvin, H M, and White, P D. A Clinical Report on the Use of Quinidine Sulphate, Arch Int Med 31 345 (March) 1923

They concluded that the danger of embolism under quinidine therapy is not much greater than with any other form of treatment

Carr³ reported seventy-seven cases of auricular fibrillation in which treatment with quinidine was given, in twenty-three of which a return to regular rhythm occurred. He stated that in not one of the twenty-three cases did an embolus develop. In reviewing one hundred hospital records of cases of auricular fibrillation Carr stated that "in sixteen instances there was a history of embolism at some time in the course of the disease."

Levy⁴ observed fifty patients with auricular fibrillation whom he divided in two equal groups. He gave the usual treatment for heart failure to group 1 and the usual treatment plus quinidine to group 2. The results were as follows. Among the twenty-five patients treated without quinidine embolus occurred in five, among the twenty-five treated with quinidine embolus probably occurred in one. He stated, too, that the danger of emboli accidents after quinidine has been given undue emphasis."

Korns,⁵ in a clinical study of quinidine sulphate in auricular fibrillation, inquired whether

the cases of embolism from this cause are more frequent than those which commonly occur in fibrillators who are being treated intensively with digitalis, or is it that we hear more of them by reason of the prominence of quinidin in the medical literature? It is my belief that the actual percentage of such cases will be found almost equally divided between the two causes. We feel it our duty to extend the benefit of digitalis to our patients, although we realize fully the likelihood of subsequent embolism. Similarly, I believe we shall find it our duty to extend the benefit of a normal cardiac mechanism without probability of greater hazard.

Bramwell and Ellis⁶ cited the following case. A man, aged 25, with rheumatic carditis of long standing, who was being treated by rest in bed and small doses of digitalis, and who apparently was making good progress, died suddenly. Autopsy did not reveal the cause of death. Bramwell stated that if this patient had been given quinidine in all probability death would have been attributed to its toxic effects.

Morawitz and Hochrein⁷ use quinidine as a prophylactic measure to prevent acute heart failure in decompensated hearts with auricular

3 Carr, J. G. The Untoward Effects of Quinidine, *Illinois M. J.* **46** 445 (Dec.) 1924.

4 Levy, R. L. Clinical Studies of Quinidin. IV. The Clinical Toxicology of Quinidin, *J. A. M. A.* **79** 1108 (Sept. 30) 1922.

5 Korns, H. M. An Experimental and Clinical Study of Quinidin Sulphate. *Clinical, Arch. Int. Med.* **31** 36 (Jan.) 1923.

6 Bramwell, J. C., and Ellis, R. The Ultimate Results of Quinidine Therapy in Auricular Fibrillation. *Lancet* **2** 960 (Nov. 10) 1928.

7 Morawitz, P., and Hochrein, M. Zur Verhütung des akuten Herztodes, *München med. Wchnschr.* **76** 1075 (June) 1929.

fibrillation They state that since they have adopted this treatment their results have been better

After considering the aforementioned investigations on the action and results of quinidine therapy, it occurred to me that the unpleasant effects that have been so often mentioned in the literature had been over-emphasized, and that a trial of quinidine in ambulatory patients with auricular fibrillation was justified

Twenty-eight patients were treated by the ambulatory method In 17 of these 28 cases or 60.7 per cent, a normal rhythm was restored If 4 patients who failed to continue treatment are eliminated, sinus rhythm was successfully restored in 70.8 per cent These results compare favorably with those obtained in many of the hospitalized patients whose cases are reported in the literature Eismayer,⁸ reporting 1,058 cases from the literature up to 1927, found that in 618, or 58.5 per cent, favorable results were obtained Burwell and Dieuaide⁹ reported that in 339, or 55.9 per cent, of 606 cases of auricular fibrillation up to 1923 a return to regular rhythm occurred More recently Carr,³ reporting 77 cases of auricular fibrillation, found that in 23 normal rhythm was restored In 1929, Wolf and White,¹⁰ in reporting 62 cases of auricular fibrillation, found that in 42, or 67.7 per cent, normal rhythm was restored

DURATION OF RESTORED REGULAR RHYTHM

In our series of seventeen cases the period of time during which the hearts remained regular after they were restored to normal rhythm compares very favorably with the cases reported by Maynard,¹¹ Harris,¹² Riecker,¹³ Viko, Marvin and White,² and Wolf and White¹⁰ Table 1 gives the age of the patients, the total amount of quinidine given, the period of treatment and the duration of the restored normal rhythm Three of the patients in the series have died since the table was compiled In one the heart was regular for twelve months, in one, for nine months and in one, for three months

8 Eismayer, G Die Behandlung Unregelmässiger Herzthätigkeit mit Chinidin, *Deutsches Arch f klin Med* **156** 182, 1927

9 Burwell, C S, and Dieuaide, F R Clinical Experience with Quinidin, *Arch Int Med* **31** 518 (April) 1923

10 Wolf, F L, and White, P D Auricular Fibrillation, *Arch Int Med* **43** 653 (May) 1929

11 Maynard, E P, Jr Five Years' Experience in the Treatment of Chronic Auricular Fibrillation with Quinidine Sulphate, *Am J M Sc* **175** 55 (Jan) 1928

12 Harris, K E A Series of Cases of Auricular Fibrillation Treated with Quinidine Sulphate, *Heart* **14** 283 (March) 1929

13 Riecker A Clinical Study of Quinidine Therapy, *Am J M Sc* **170** 205, 1925

ETIOLOGY

In relation to etiology, this series of cases was divided into six groups. Table 2 gives the number of cases restored to regular rhythm and the average ages.

TABLE 1—*Duration of Restored Normal Rhythm*

Name	Age	Total Amount of Quinidine Given, Gm	Duration of Treatment, Days	Duration of Restored Normal Rhythm, Months
Mr Os	66	6.6	7	12
Mr Ov	53	9.4	11	2
Mr McK	62	12.5	28	7
Mrs B	31	45.6	35	1
Mrs Ha	70	24.2	49	10
Mrs M	62	4.2	14	16
Mr O'B	69	34.7	54	2
Mr A	73	19.2	26	3
Mr W	66	3.8	5	3
Mr S	61	45.6	61	6
Mr F	74	18.9	27	2
Mr B	73	0.6	1	3
Mrs H	37	76.4	107	7 days
Mrs M	46	3.0	7	2
Mrs G	62	2.4	3	Cannot be traced
Mr L	59	4.8	10	9
Mr P	67	1.8	7	2

TABLE 2—*Etiology of Cases of Auricular Fibrillation*

Etiology	Number	Normal Rhythm Restored	Average Age of Those Restored to Normal Rhythm	Average Age of Failures
Rheumatic valvular heart disease	5	4	45.7	26
Hypertension and coronary sclerosis	14	10	63.5	58.5
Hyperthyroidism	1	0		
Hypertension and diabetes	2	1	70	55
Aortitis	1	1	62	
No apparent heart disease	1	1	73	

TABLE 3—*Ages in Decades*

Age	Those Successfully Treated		Those Unsuccessfully Treated	
	Number	Percentage	Number	Percentage
20 to 29	0		1	14.3
30 to 39	2	11.8		
40 to 49	1	5.9	2	28.6
50 to 59	2	11.8	2	28.6
60 to 69	8	47.0	1	14.3
70 to 79	4	23.5		
80 to 89	0		1	14.3

The youngest patient, Mrs F, aged 26, who had a rheumatic valvular heart disease, failed to respond to quinidine.

Over 80 per cent of the patients successfully treated were 50 years of age and over. In the unsuccessful group three were below the age of 50 and four were over the age of 50. It has been shown by several investigators that age is not an important factor for the successful action of quinidine.

SEX

In this series fifteen were males and nine females, of the seventeen in whom the heart became regular twelve were males and five, females. Of the patients in whom failure occurred, four were females and three, males. The heart beat became regular in twelve of the fifteen males, or 80 per cent and in five of the nine females, or 55.5 per cent.

DURATION OF FIBRILLATION

In all but one of the cases studied chronic fibrillation occurred. In Mr. B., aged 73, an auricular fibrillation developed after the injection of a foreign protein for arthritis. Fibrillation had been present for two days and 6 grains (0.4 Gm.) of quinidine sulphate (2 grains [0.13 Gm.] every two hours for three doses) restored the heart to regular rhythm. In more than 60 per cent of the cases, fibrillation had been present for more than one year. In two cases fibrillation had been present from ten to twelve years. The rhythm of the heart beat in one of the latter became regular.

METHOD OF TREATMENT

All patients are first given digitalis, preferably for a few days. If the heart is decompensated the patient is well digitalized until there is evidence that the heart is fully compensated, or nearly so. Quinidine is then given in small doses. The first day 0.1 Gm. is given, the following day 0.2 Gm., and the third day 0.4 Gm. The patient is given 0.4 Gm. per day for five days. Every two hours 0.1 Gm. is taken. At this point the dose of digitalis may be reduced or discontinued, depending on the degree of cardiac compensation and the heart rate. On the seventh day the dose of quinidine is increased to 1 Gm. per day, 5 grains (0.324 Gm.) every two hours until three doses have been given. After a few days, if necessary, the dose is increased to 20 grains (1.3 Gm.), 5 grains being given every two hours until four doses have been administered, then the dosage is increased to 30 grains (1.95 Gm.), 10 grains (0.65 Gm.) every two hours. As much as 40 grains (2.6 Gm.) per day was given in 10 grain (0.65 Gm.) doses at two hour intervals. As soon as the rhythm of the heart becomes regular the dose of quinidine is reduced, and a maintenance dose is established. This amount may be about 10 grains per day for several days, then 5 grains in single doses. Most of the patients are given 5 grains daily, and many are given 5 grains every other day.

In the series treated quinidine was seldom discontinued when the patient complained of the following symptoms: slight headache, diarrhea, nausea or vertigo. With the possible exception of one case, in no

instance were the toxic symptoms of quinidine so pronounced that the drug had to be discontinued

FAILURES

In seven cases, including two in which accidents occurred, the heart failed to be restored to normal rhythm

CASE 1—History—Mr R, aged 49, reported to the dispensary on Oct 27, 1930, complaining of shortness of breath, swelling ankles, vertigo, cough, hemoptysis and pain in the neck and in the upper right quadrant of the abdomen. He had been in the University Hospital and the Minneapolis General Hospital three times since 1928, each time from one to three months. The previous history was irrelevant except that he had had "rheumatic fever" at the age of 26.

Examination—Physical examination showed slight pitting of the skin of the legs. The liver was enlarged about 4 cm below the costal margin, it was soft and slightly tender. The heart was enlarged, an orthodiagram showed transverse diameter of the heart, 19.1 cm, of the chest, 28.5 cm. The heart rate was irregular, the apical rate, 100, the radial rate, 84. The vital capacity was 2,300 cc, 68 per cent of the calculated norm. The blood pressure was 180 systolic and 100 diastolic. An electrocardiogram showed arborization block and auricular fibrillation. The patient was given 1 cc of tincture of digitalis three times daily, and he reported back on October 29 improved.

Course—The patient was told to continue to take digitalis and to take 0.1 Gm of quinidine that afternoon (October 29), 0.2 Gm the next day and 0.3 Gm the third day. That night, a severe attack of pain over the precordium and marked dyspnea developed. The patient was sent to the Minneapolis General Hospital, where he died the next day. The diagnosis at autopsy was hypertrophy and dilatation of the heart, coronary thrombosis and myocardial infarction. Microscopically, the material in the coronary vessels was thrombosed, no mural thrombi were found. This death can hardly be attributed to quinidine. It was the opinion of the pathologist that it was only a coincidence that death occurred after the administration of the drug.

CASE 2—History—Mrs H, aged 37, had not been well since October, 1929, when she had had pneumonia. She had been in the University Hospital for five weeks in 1929 and again in 1930 for heart disease. On Aug 9, 1930, she came to the dispensary complaining of dyspnea on exertion. The patient gave a history of rheumatism at the age of 16.

Examination—Examination of the heart showed it to be of a double mitral type, and was enlarged. An orthodiagram showed transverse diameter of the heart, 14.2 cm, of the chest, 25.2 cm. An esophagram showed a definite displacement of the esophagus by the left auricle. The apical pulse rate was 116, the radial pulse rate, 104. The blood pressure was 150 systolic and 106 diastolic. The patient was given digitalis until Sept 22, 1930, when quinidine sulphate was added.

Course—Small and increasing doses of quinidine were given until Jan 7, 1931, when the pulse was regular for the first time. An electrocardiographic report showed 66 beats per minute, regular, and delayed auriculoventricular conduction.

The heart rhythm was regular until Jan 14, 1931, when I was called to the patient's house. There was complete paralysis of the right side of the face, arm and leg. The pulse was totally irregular. I do not know for how long it had been irregular or whether the hemiplegia occurred before the heart rhythm became irregular or afterward.

SUMMARY

1 Twenty-eight cases of auricular fibrillation in which the patients were treated with quinidine are reported, four did not continue treatment, so that only twenty-four were treated satisfactorily by the ambulatory method

2 In seventeen cases, 70.8 per cent of the twenty-four in which treatment was satisfactory, normal rhythm was restored

3 Of the successfully treated patients, four had rheumatic valvular heart disease, ten had hypertension and coronary sclerosis, one had diabetes and hypertension, one had syphilitic aortitis, and one had an apparently normal heart

4 Eighteen of the twenty-four patients were 50 years of age or over, in fourteen of this group, or 77 per cent, the heart was restored to regular rhythm. In three of the remaining six patients regular rhythm was restored

5 The group with hypertension seemed to respond more quickly than the rheumatic group

6 In all but one there was chronic fibrillation for from two months to ten or twelve years

7 In the treatment small doses of quinidine were given to start with, then the dose was gradually increased

8 Tincture of digitalis was always given first or in conjunction with quinidine during treatment

9 Two accidents occurred during treatment: one death from coronary thrombosis and a case of hemiplegia

ENCEPHALOPATHY DUE TO CHRONIC PLUMBISM

REPORT OF A CASE

THEODORE S EVANS, M D

NEW HAVEN, CONN

Since the monumental work of Aub and his co-workers¹ on lead poisoning, all reports of cases seem dwarfed into insignificance. However, the following reasons justify the case herewith published

- 1 Good results were obtained from mobilization treatment
- 2 "Deleading" resulted in a syndrome similar to tetany on two occasions, in each of which intravenous administration of calcium was immediately and spectacularly effective
- 3 The case was not associated with hypertension

REPORT OF A CASE

History—L. H., aged 48, a plumber, complained of inability to coordinate, particularly in walking. His wife said that he was mentally confused and irritable. He had worked as a plumber many years and had handled considerable red lead. He had also been in many new houses where painting was being done, and had worked a good deal with boiling lead. Therefore, there was a possibility of poisoning from the gastro-intestinal tract, or by droplets and fumes from the respiratory tract.

Until four years before examination the patient had been very well, but at that time he was seized with severe cramps in the abdomen, vomiting and diarrhea, which was symptomatic of lead colic, though a diagnosis was not made. Presently the pain, vomiting and diarrhea disappeared, but he began to have pain in the muscles, which he thought was due to "rheumatism." The muscular pains had continued. They were worse in the calves of the legs and in the back. The patient also noticed that during the four years previous to examination, he had dropped his tools frequently, and had not been able to use them with his usual skill.

There was a gradually increasing weakness of the legs which became nearly a paralysis in November, 1926 (seven months before examination), and about the same time the patient noticed severe headaches and twitchings of the arms and legs, greatly aggravated by fatigue. There has been marked propulsion and a very decided tendency to fall to the left side. This twitching progressed gradually until he was unable to walk. He was very drowsy and yawned interminably. His wife stated that he was very irritable and disagreeable, and that his memory was extremely poor. He was immensely confused, and at times completely disoriented.

Submitted for publication, July 15, 1931

This case was presented before the New Haven Medical Association in June, 1928

1 Aub, J. C., and others. Lead Poisoning, *Medicine* 4 1, 1925

There was some blurring of the vision, which has gradually cleared up until he was able to see well. His appetite had been poor, and he had been constipated.

There had been nycturia once a night and once he passed some blood. He had a great deal of difficulty in starting the urinary stream.

The past history was irrelevant, except for work as a plumber. The patient had been an extremely strong man, able to beat all his companions in rough and tumble fights. His weight had been stationary, and his habits good. He said that he had never had a venereal disease.

He had been to a number of physicians who considered various diagnoses including brain tumor, epidemic encephalitis, syphilis and autointoxication. He was seen at the Yale Mental Hygiene Clinic, and a diagnosis of lead encephalopathy was made by Dr. C. C. Fry. Potassium iodide was given for four days for elimination of lead. Lead was found in the stools and urine.

Physical Examination—The patient appeared well developed and well nourished. There was no cyanosis or dyspnea. The skin showed a very pasty color. The temperature was 98 F., pulse rate, 76, blood pressure, 120 systolic and 80 diastolic, and weight, 170 pounds (77.1 Kg.).

The eyes reacted to light promptly. The eyelids showed no ptosis. The eye-grounds were normal.

The teeth showed some caries and several were loose. There was a "lead line" on the gums. Roentgenograms of the teeth were negative. The tonsils were small with no pathologic process. The neck was normal.

The heart was slightly enlarged to the left, and the second aortic sound was rather loud.

The lungs showed numerous small râles rather evenly distributed. No other signs were present.

The abdomen was normal, and there was no tenderness or masses.

The extremities were normal.

The reflexes were all exaggerated, but all were present and about equal.

The blood vessels were not palpable.

The glandular system was normal.

Marked weakness was noted in all muscles, particularly in the calves and thighs. The patient could not walk, and if left alone fell to the left or forward. He could not even sit up by himself.

He was mentally confused, and did not remember the day or the month. He remembered very little of what happened the day before, was irritable and fell asleep while I was taking the history.

Laboratory Examination—Lead was found in the urine and feces, at the New Haven Hospital. Hemoglobin was 85 per cent, red blood cells numbered 4,500,000, white cells 6,000 and polymorphonuclears 65 per cent. The smear showed no stippling or secondary anemia. The Wassermann reaction of the blood was negative. Routine examination of the urine gave negative results except for a slight trace of albumin which later cleared up. The spinal fluid showed cells, 25, colloidal gold curve, 00004555430, phthalein, 75 per cent, nonprotein nitrogen, 29 mg., Wassermann reaction, negative, and globulin, negative. Lead was not present.

Treatment—Syrup of hydriodic acid, 4 cc. (1 fluid drachm), was given every three hours for four days. Lead was now found in the feces and urine. After four days this treatment of elimination was discontinued. Mobilization was attempted by the use of calcium chloride and milk (calcium lactate, 1 Gm. twice a day and 2 quarts of milk a day).

For the first three weeks improvement was slow but steady. The mental symptoms began to clear, and the patient's memory returned slowly. There were

five days of regression and then, suddenly, in the fifth week of the treatment he got up out of bed one morning, shaved himself and began to walk. After that he continued to walk by himself, and his memory was almost normal. I considered that I had mobilized the lead in the bones, at this point, as trilead phosphate.

In May, 1927, the "lead line" was absent. There were no stippled cells. The hemoglobin was 80 per cent, and the red blood cells 5,000,000. The urine contained no lead.

When the patient began to be fatigued, twitching of the muscles occurred, but at all other times he had no more subjective symptoms.

From May, 1927, until January, 1928, the patient continued doing well without episodes of any kind. The urine and feces were clear of lead on several occasions. The patient continued to gain strength and coordination, so that by fall he was able to do all types of work. Owing to the fact that the change in the hydrogen ion concentration might be induced by some casual illness as acute tonsillitis, grip, pneumonia or the like, it was felt that the man should be "delead." It seemed that "deleading" by the use of diet and drugs would be more simple to control than to attempt to cope with a sudden "deleading." A diet very low in calcium, which omitted milk, eggs, green vegetables and fruit and consisted of meat, liver, potato, rice, tomato, canned corn, bananas, apples, tea, coffee and all foods prepared without milk, such as salt-free nephritic bread, sodium bicarbonate bread or crackers, was prescribed. Sugar, salt and pepper were allowed. With this diet ammonium chloride, 1 Gm, ten to twelve times a day in a glassful of water was also given. The diet proved very efficacious in "deleading," for after three days of the diet and medication lead was found in the urine and feces. The patient was discharged from the hospital after about two weeks of the treatment and went home, continuing the diet with ammonium chloride until February 25, when the ammonium chloride was discontinued. During that period, he had no toxic symptoms, and lost that "aching feeling" in his muscles and joints.

Course—On March 10, 1928, the patient was feeling better than he had felt any time in the past six months. Four examinations of the urine between January, 1928, and March, 1928, showed no lead.

On March 10, the patient went to a club meeting and ate pickles, cheese, fresh peaches, rye bread and drank beer and wine. He drove his car to and from the meeting, a friend who went with him thought he acted a bit peculiarly. He went to bed and in the morning about 6 o'clock, his wife noticed that he was breathing heavily. Thinking that it was merely a sound sleep, she did not wish to disturb him, but on entering the room at 9 o'clock, she found him in the midst of a convulsion and immediately called me. It was about an hour and a half before I could reach the patient's home. When I arrived, he had already had eight convulsions and some probably previous to the time that his wife entered his room. A physician who had been called in the interim was giving him a hyperdermic of morphine. The convulsions were severe, tonic and clonic convulsions, and were followed by a long period of apnea during which time he became unbelievably blue, although the pulse stayed fairly strong except during one convulsion when it became weak and thready.

Each convulsion began with twitching of the muscles of the eye on the right side resulting in an upturning of the lids and proceeded to involve the entire body. The pupils were widely dilated in spite of the use of morphine and did not react to light. The eyegrounds showed constriction of the retinal arteries, but otherwise were normal. The eyes were turned upward and inward. These convulsions were followed by periods of apnea, one of which measured nearly three minutes by the watch. During these periods artificial respiration was given. During one of the

early convulsions, he had bitten his tongue badly and the bed was covered with blood. There was evidently also incontinence of both feces and urine during one of the convulsions. Between convulsions, Chvostek's and Trousseau's signs could be elicited easily. The eyegrounds were normal. Physical examination revealed no lesion in the lungs or heart, nor, so far as we could perceive, in the abdomen. The blood pressure was 110 systolic and 70 diastolic. Serum calcium was 7.5 mg and nonprotein nitrogen 32.

I went immediately to Grace Hospital and obtained 60 Gm of calcium chloride ready for intravenous administration. This was given to the patient intravenously. Following this the stomach was washed out, and in the contents we recovered the remains of pickles which he had eaten the night before. Following this procedure, a pint of milk was left in the stomach by gavage. A spinal puncture was done, and although the fluid was under pressure it was negative for globulin and for cells, and the Wassermann reaction was negative. Colloidal gold also proved normal. Fifteen cubic centimeters of fluid was removed. Sixty units of parathyroid hormone was also given intravenously with the idea that possibly the calcium might be more quickly utilized by the use of the hormone. He also had two doses of $\frac{1}{150}$ grain (0.4 Gm) of hyoscine hydrobromide.

Following the intravenous administration of calcium and the parathyroid hormone the patient had three convulsions, the first of which was as severe as those he had preceding this medication, the last two were noticeably less severe, he also had three very mild convulsions. From 1 o'clock on he had no more convulsions.

He was moved to Grace Hospital by ambulance, at 4 p. m. He started to move his arms purposefully about 6 in the evening, and at 9 he was able to make it evident by signs that his bladder was distended. He was catheterized and 1,500 cc of urine obtained. This specimen did not contain lead and was normal in all respects.

The following morning he was able to speak, but thickly, because of the lacerated and swollen tongue, but it was evident that he understood perfectly everything that was said and could have spoken clearly except for the injury to his tongue. He remembered what had happened two nights previously, but nothing of what happened the previous day. He had a temperature for a few days, which was assumed to be due to the infection in his tongue, because as soon as the infection cleared up the temperature disappeared. Physical examination at that time gave negative results, except for ptosis of the left eyelid and the bitten tongue. The blood pressure was 115 systolic and 70 diastolic. The patient was put on calcium lactate and made an uneventful recovery.

In September, 1928, he was feeling better than at any time in the past five or six years. The pains were completely gone from his muscles and bones. He had no incoordination or confusion, and his personality was what his friends claim it used to be.

From the attack of convulsions in March, 1928, until September, 1928, the patient's condition was good. He was able to do ordinary labor such as chopping wood, to complete his inventory, to do accounting in his business and to drive his automobile.

From September, 1928, until December, 1928, the patient's condition became gradually less good. He was seen at various intervals with steadily increasing neurologic signs. Headaches became a permanent feature. They were severe and explosive, beginning with dulness and reaching a crescendo. At these times he was confused, and memory was difficult. The reliefs from the headaches were sudden, and they were usually improved by rubbing the back of the neck. At vari-

ous times following these headaches, he showed right-sided hemianopia. The blood pressure had been low from September to December, 1928, being around 110 systolic and 70 diastolic to 125 systolic and 75 diastolic. The nonprotein nitrogen had been 30, the plasma chloride, 550.

About December 14, the patient had an acute diarrheal disease for which he did not call me. Four days later, December 18, I was called. For the past four hours the patient had had convulsions similar to those that occurred in March, 1928. They began with twitching of the muscles of the right eye, resulting in the upturning of the lids and deviation of the eyes and head to the right. The pupils were widely dilated during the periods of convulsion. The periods of apnea were of about the same length as those in March, and between the convulsions artificial respiration was given. Between the seizures, speech was difficult, sometimes amounting to complete aphasia. The eyegrounds showed constriction of the retinal vessels. No evidences of meningeal irritation were noticed. Cyanosis was as deep as in March. The blood pressure was 120 systolic and 70 diastolic. The heart and lungs were normal. Nonprotein nitrogen was 32, plasma chlorides, 560, and serum calcium, 6.5 mg. The urine was normal. These attacks endured for twenty-four hours in spite of treatment.

The diagnosis at this time was a degenerative process in the brain, directly or indirectly, the convulsive seizures seemed related to the calcium deficiency in the blood. Consultation with Dr. James Fox corroborated these findings, and he gave his impression:

"The condition is a degenerative process in the brain. The nature of vascular occlusion is directly associated with the chronic plumbism which is thought to be responsible for the clinical picture." The chief irritative lesion was assumed to be in the left hemisphere. In view of both the irritative and paralytic phenomena to the right side, large sedative and antispasmodic medication was advised, including inhalants (ether and chloroform). This treatment was carried out without beneficial effect.

The following day, as treatments had been ineffective for forty-eight hours, and since the serum calcium was so low, intravenous injection of calcium, 60 grains (3.9 Gm.), was given, purely empirically, because it had accomplished such spectacular results in March, although the patient was at this time on a high calcium diet. The result was as spectacular this time as it had been in March, 1928.

The patient made a complete recovery from the convulsions shortly after the calcium was given.

In looking backward on the case, it seems that the cause of these convulsions was tetany just as in March, 1928, and at this time it was a case of tetany due to inability of an inflamed intestinal tract to absorb calcium even with the patient on a high calcium diet. Examination of the spinal fluid obtained at this time was negative in all respects. Urine obtained at this time showed no lead.

Following the convulsion in December, the patient finally recovered partially but never was able to do more than walk about the house, attend to his own habitual needs and occasionally go for a ride in the automobile or to shave. The improvement was slow, but apparently there was an upward trend to it. Roentgenograms of the teeth were made and found to be negative. The eyegrounds showed paralysis of the muscles and slight pallor of the optic disks. The patient was seen by Dr. Arthur Alling, who confirmed these findings. In June, 1929, he was at the point where he could be roused with difficulty and only for a short time. He was then seen by Dr. George Blumer, who corroborated the diagnosis of multiple central nervous system lesions due to lead.

From June to September, the patient made a slow but steady improvement. In September, 1929, he developed what was apparently severe bronchitis and general infection of the upper respiratory tract. I was away at this time, and Dr Israel Blodinger cared for him during my absence.

During this attack, the patient lost a tremendous amount of ground. He lost a great deal of weight, and when next seen in November, 1929, found it impossible to walk, because of incoordination and weakness of the muscles. It was difficult for him to swallow food, and the act was very slow. This was probably due to muscular weakness and incoordination. He was very stuporous and could hardly be aroused. He showed all of the neurologic manifestations which were noted before, and at this time none were transitory. He was seen in November by Dr Joseph Aub, of Boston. Dr Aub's diagnosis was also chronic lead poisoning with multiple lesions of the central nervous system.

On the basis of the past history and findings, Dr Aub recommended that intravenous calcium therapy be tried again, considering that perhaps the man was unable to absorb calcium even though he was getting fair doses of it into the stomach. This suggestion was carried out but he did not improve. Bronchopneumonia developed and he died with high temperature, increased pulse rate and respiratory rate, after a few days of treatment.

Autopsy was refused in spite of every effort.

COMMENT

The diagnosis in the case seemed very clearly to be lead poisoning. Lead was found in both feces and urine. The encephalopathy was apparent in the history and physical examination. In the light of subsequent events, it was considered possible that there may have been multiple sclerosis all the time. But this does not seem tenable, particularly as rational treatment for lead poisoning removed all symptoms for a time. That multiple lesions of the spinal cord and brain later developed is perfectly apparent, but I believe they were caused by lead poisoning, itself.

The reason for these attacks of convulsive and explosive nature is not clear. Certainly there is no evidence of arteriosclerosis in the general physical examination, nor in the examination of the eyes, and there was no hypertension. Examination of the urine showed normal concentration and the blood chemistry was normal throughout the course, the nonprotein nitrogen and plasma chloride figures were normal. Therefore, uremia cannot be said to explain the picture.

During the discussion before the New Haven Medical Association it was suggested that acidosis might account for the convulsive seizures, but there was no ketonuria or other findings at these times suggestive of acidosis. In addition to these negative findings, the following signs of tetany could not be explained by a simple acidosis. Apparently the calcium depletion seemed to have some direct or indirect relationship to the state.

1 The patient was on a low calcium diet at the time of the first seizure

2 At the time of each seizure, the serum calcium was low

3 On both occasions, Chvostek's and Trousseau's signs were present

4 Spectacular and immediate results were obtained from the use of intravenous calcium

That there was a temporary increase in intracranial pressure would seem evident from the fact that the spinal fluid was under marked pressure at both times of seizure. Probably there was a marked cerebral edema similar to that described by Blackfan,² Rees,³ Volhard⁴ and others.

Vasoconstriction with temporary cerebral anemia was probably the direct cause of the convulsive seizure and resulted from cerebral edema. This symptom complex has been noted by various observers—Elschnig,⁵ Wagener,⁶ and Smith⁷—who in studying the eyegrounds during convulsions found constrictions of the retinal vessels similar to that which was found here. Although such authorities as Traube⁸ and Vaquez⁹ stated that arterial hypertension is always present in lead encephalopathy, it was not found in this case, nor was there present any crescendo increase in blood pressure, such as was described by Oppenheimer¹⁰ and Fishberg, just previous to the convulsive seizures.

It is also noteworthy that the patient did not die in a convulsive state. His course was gradually downward for the period of a year after the last convulsive state, and he died of bronchopneumonia, with evidence of marked degenerative lesions of the brain and spinal cord. The question of the relation of treatment to the convulsive seizures is interesting, but uncertain. It is apparent that lead mobilization was effective for the man made nearly a complete recovery during the treatment. The "deleading" was successful as considerable quantities of lead were poured out in the urine during the process, and then came to a period, during treatment, when no lead appeared in the urine.

2 Blackfan, K. D. *Bull. Johns Hopkins Hosp.* **39**: 69, 1926.

3 Rees. *On the Nature and Treatment of Diseases of the Kidney*, London, 1850, p. 67.

4 Volhard. *Der arterielle Hochdruck*, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**: 134, 1923.

5 Elschnig. *Wien. med. Wchnschr.* **48**: 1305, 1898.

6 Wagener, reference deleted.

7 Smith. *Brit. M. J.* **2**: 1380, 1909.

8 Traube. *Ges. Beitr. z. Path. u. Phys.* **2**: 551, 1871.

9 Vaquez. *La tension artérielle dans le saturnisme aigu et chronique*, *Semaine med.* **23**: 385, 1904.

10 Oppenheimer, B. S., and Fishberg, A. M. *Hypersensitive Encephalopathy*, *Arch. Int. Med.* **41**: 264 (Feb.) 1928.

The "deleading" treatment was apparently carried further than was desirable in that it produced a calcium depletion and led directly or indirectly to the convulsive seizures in the first instance. However, the complete recovery of the patient from this state and the absence of all symptoms for a long period after this incident appear to indicate that this was not contributory to his demise.

The second convulsive state could not be attributed to treatment as the patient was at the time on a high calcium diet and therapy, although it is probable that a diarrheal disease made it impossible for him to utilize the calcium ingested. His recovery from the second convulsive state was complete so far as tetany was concerned, and he never showed any further symptoms of this condition.

In the light of the entire findings in the case it would seem that the patient died of a gradually increasing encephalopathy caused by chronic plumbism. The early central nervous lesions of this condition gradually progressed and were the cause of death.

SUMMARY

1925, summer The patient had an attack of lead colic.

1925-1927 Increasing muscle weakness and pains of myositis were noted.

1926, November Symptoms which had been present to a slight degree for a long time were aggravated, i. e., loss of appetite, mental confusion, loss of memory, disorientation, irritability, loss of coordination, particularly in walking, drowsiness, vertigo and headache.

1926, December Bloody urine was passed and from then until April the patient found it difficult to start the urinary stream. Albumin was present throughout this period but then cleared.

1927, April Physical examination and laboratory findings showed lead poisoning (November and December notes.)

1927, May The patient's mental condition cleared up, and most of the symptoms and physical signs of lead poisoning disappeared. All laboratory findings were negative.

May to July There was disappearance of all symptoms except muscular pains, the patient stated that he "felt lead in his bones."

July to January, 1928 The patient gained in strength so that he was able to do quite heavy work but still had muscular pains.

January "Deleading" was done at Grace Hospital. A low calcium diet with ammonium chloride in large doses was given, lead was again found in the urine at this time for a period of ten days. No episodes of any kind occurred.

March 10 For the first time the patient felt entirely well. The muscular pains disappeared. Four examinations of urine and feces were negative for lead.

March 11 Convulsions with apnea, coma and tetany occurred. These were promptly relieved by the intravenous administration of calcium and parathyroid hormone. The patient was again sent to Grace Hospital. He was put on a high calcium diet, and given calcium lactate by mouth.

March 18 The patient's mental condition cleared up, and he said that he felt well in every respect. Friends corroborated this statement.

December The patient had a diarrheal disease for which he did not call me. Five days later, the convulsions, apnea, coma and tetany again developed. All types of sedative, including ether, were used but did not avail. Intravenous calcium again was effective. The patient recovered in part but not entirely. He showed some right-sided muscular weakness for about one week, and then this cleared. He was able to tend to his personal needs.

December to May, 1929 There was a slow but steady improvement. The patient was able to get out in his car.

May to June There was a period of decline, so that in June the patient could only be roused with difficulty. He was still on calcium therapy.

June to September There was a slow but steady gain, so that the patient was better than in June but not yet able to do much more than ride in a car.

September He had an acute disease of the upper respiratory tract. He was under the care of another physician and lost a great deal of ground.

November He never recovered completely from the infection in September, and late in November he developed bronchopneumonia and died.

SPONTANEOUS NEPHRITIS IN THE RABBIT

CHANGES IN THE URINE, BLOOD METABOLITES, PHTHALEIN EXCRETION
AND BLOOD PRESSURE IN A GROUP OF TWENTY ANIMALS
FOLLOWED FOR A PERIOD OF THREE YEARS

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During the hundred and twenty years from 1800 to 1920, there was in the United States a gain of twenty-five years in the average expectancy of life. In the two decades from 1900 to 1920, there was a gain of five years. The average expectancy of life at the present time is 55.33 years for white males, and 57.52 years for white females. The chief statistical cause for the increase in life expectancy has been the saving of infant and child lives, but there has been an actual increase in the life expectancy of adults. As a result of the increase in the average span of life, a larger number of persons are entering the later decades when the so-called degenerative diseases take their toll. These diseases are chronic nephritis, degenerative heart conditions and hypertension. These three groups, which are closely related in both an etiologic and a pathologic sense, were responsible for 45.5 per cent of the deaths of persons beyond 45 years of age in the United States during 1920¹. It is evident that a further prolongation of the span of life must concern itself with a delay in the onset of degenerative diseases and a prolongation of their course in those who have already developed them.

Since the classic descriptions of Bright in 1827, the etiology of chronic renal disease has challenged increasing attention. Of the numerous theories, that which postulates renal damage as resulting from a long-continued, high protein intake has attracted most attention, in part because protein catabolites are excreted almost entirely by the kidney. An extensive literature has accrued both for and against this thesis.

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1 Statistical Bulletin, Metropolitan Life Insurance Company 8:1 (Nov.) 1927

Experimental results have been conflicting Osborne, Mendel and their associates² fed diets, of which protein contributed two thirds of the total calories, to rats for as long as four hundred days Wheat, corn and casein were used The kidneys of these animals were uniformly hypertrophied and the tubules dilated, but no true nephritis was produced Jackson and Riggs,³ in experiments of a similar nature, fed a 76 per cent casein diet to rats for as long as twenty months and reported negative results The experiments of Addis, MacKay and MacKay,⁴ in which diets of 69.5 per cent protein were fed to rats over a period of one third natural life, were in apparent confirmation of these results Recently, Parsons, Smith, Moise and Mendel,⁵ in an investigation primarily of the effect of the protein content of the diet on the reproductive cycle of the rat, found that a high protein content, even after unilateral nephrectomy and the added burden of gestation and lactation, caused only physiologic hypertrophy of the kidneys Similarly negative results have been reported by Anderson,⁶ who fed rabbits a diet of from 55 to 60 per cent beef protein for periods as long as one year In some of the animals varying amounts of renal tissue were removed Hypertrophy of the kidneys or kidney remnants resulted, but no evidence of nephritis was discernible

On the other hand, experiments in which the results were strikingly positive have been reported Moise and Smith⁷ regularly produced renal lesions in rats as soon as ninety days after unilateral nephrectomy when fed a high protein diet The nephritis was apparently of a diffuse type Polvogt, McCollum and Simmonds,⁸ by diets entirely sufficient for growth and maintenance and deficient only in containing from 31 to

2 Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C. Physiological Effects of Diet Unusually Rich in Protein or Inorganic Salts, *J Biol Chem* **71** 317 (Jan) 1927

3 Jackson, H. J., Jr., and Riggs, M. D. Effect of High Protein Diets on Kidneys of Rats, *J Biol Chem* **67** 101 (Jan) 1926

4 Addis, T., MacKay, E. M., and MacKay, L. L. The Effect on the Kidney of the Long Continued Administration of Diets Containing an Excess of Certain Food Elements *J Biol Chem* **71** 139 (Dec) 1926

5 Parsons, H. T., Smith, A. H., Moise, T. S., and Mendel, L. B. Reproduction and Excess Protein in the Diet, *Arch Path* **10** 1 (July) 1930

6 Anderson, H. Experimental Renal Insufficiency Effects of High Protein Diet in the Presence of Low Renal Function on the Kidneys, Aorta, and Liver, Changes in the Blood Pressure and Concentration of Blood Metabolites, *Arch Int Med* **37** 297 (March) 1926

7 Moise, T. S., and Smith, A. H. The Effect of High Protein Diet on the Kidneys, *Arch Path* **4** 530 (Oct) 1927

8 Polvogt, L. M., McCollum, E. V., and Simmonds, N. The Production of Kidney Lesions in Rats by Diets Defective only in That They Contained Excessive Amounts of Proteins *Bull Johns Hopkins Hosp* **34** 168 (May) 1923

41.3 per cent protein, regularly produced casts and intense congestion of the kidneys. They regarded the high protein diet as nephrotoxic.

Newburgh and his co-workers,⁹ in carefully conducted experiments over long periods of time, have produced renal lesions of a degenerative character in both albino rats and rabbits by using diets rich in casein, liver,^{9a} beef, egg white and soy bean. They concluded that the severity of the lesion depended more on the duration of the experiment and the nature of the protein than on its amount. Urea added to the diet was innocuous, which suggested that the nephropathy was not the result of a nonspecific increase in the nitrogen metabolism. The renal lesion was primarily confined to the tubules. However, in the rat, a 72 per cent beef protein diet caused definite glomerular changes. Similar results in the rabbit have been reported by other observers¹⁰ using a casein diet.

In previous experiments,¹¹ we have been able to confirm these positive results. On using both animal and vegetable protein (liver diet, 40 per cent protein, oat diet, 16 per cent protein, soy bean diet, 38 per cent protein) in feeding experiments with rabbits extending over a period of two years, we found a high incidence of chronic nephritis and arteriosclerosis. This nephritis was characterized by persistent urinary abnormalities, retention of nitrogen end-products in the blood and elevation of blood pressure.

On examining these data in retrospect it was thought that the experiments could be criticized on the ground that the pathologic alterations might have arisen spontaneously. A study was therefore undertaken to answer the following questions:

1. Are spontaneous renal lesions of common occurrence in the rabbit?
2. Are they distinguishable pathologically from experimentally produced lesions?
3. Are they of sufficient magnitude to cause disturbances in the body economy of the living animal?
4. Will an experimentally fed high protein diet exaggerate a spontaneous nephritis?

9 Newburgh, L. H., and Curtis, A. C. Production of Renal Injury in the White Rat by Protein of the Diet, *Arch Int Med* **42** 801 (Dec.) 1928. Newburgh, L. H. The Production of Bright's Disease by Feeding High Protein Diets, *ibid* **24** 359 (Oct.) 1919.

9a Newburgh and Johnson, in a recent paper (*J Clin Investigation* **10** 153, 1931), stated that a 20 per cent sodium nucleate diet is nephrotoxic in less than a year. The sodium nucleate was prepared from liver, but the changes produced were qualitatively different (fibrous tissue proliferation, changes of the arteriolar walls) from those that result from feeding liver. It is concluded that liver contains forms of nonprotein nitrogen other than purines which are nephrotoxic.

10 Maclean, H., Smith, J. R., and Urquhart, A. L. Effect of High Protein Diet on Renal Function, *Brit J Exper Path* **7** 360 (Dec.) 1926.

11 Nuzum, F. R. Changes in the Kidney in Animals with Increased Blood Pressure While on High Protein Diets, *Arch Int Med* **40** 364 (Sept.) 1927.

We have previously described two distinct pathologic types of spontaneous renal lesions encountered in the routine histologic examination of the kidneys of a hundred and ninety supposedly normal animals¹² The first type was a focal scarring which gave no evidence of its presence during life and which occurred only twice (an incidence of 1 per cent) in this group of animals It may be disregarded The second type was very different It was a diffuse lesion, involving to some extent all of the renal structure It also occurred only twice in this group of one hundred and ninety normal animals However, in a group of twenty animals comprising the present study, which were selected during life because of persistent urinary abnormalities, this diffuse nephritis was the pathologic change It was morphologically indistinguishable from the nephritis that we had previously produced by feeding high protein diets In the present study we wish to trace the development of this spontaneous renal lesion in these twenty animals It will be shown (1) that the clinical and laboratory features are similar to those characterizing the nephritis produced by high protein diets, and (2) that the feeding of a high protein diet to animals already having this lesion will increase the renal damage

From a total of two hundred and fifty rabbits, twenty full grown animals were selected because of the repeated presence in their urine of albumin, casts and cylindroids They varied from 6 months to 1 year in age, and were kept in outdoor hutches the year around They were observed for a period of thirty-six months

During the first year the animals were fed a diet of barley, 85 Gm, and alfalfa, 50 Gm, daily, with the addition of other greens twice each week This diet was so balanced that the reaction of the urine of these animals was neutral or slightly alkaline, the p_H averaging 7 During the second year of the experiment the p_H averaged 8.5, owing to the fact that it was necessary to feed alfalfa ad libitum to the animals to keep them in good condition During the third year, ten of the animals were placed on a liver diet suggested by McCollum⁸ and used by us in previous experimental work This diet was devised as being adequate for nutrition The addition of the ground liver made a high total protein content resulting in the passage of acid urine with an average p_H of 6.2 We had previously found that the continued feeding of this diet over a long period of time resulted in an increase in blood pressure and the development of arteriosclerosis and chronic nephritis This diet was

12 Nuzum, F. R., Elliot, A. H., Evans, R. D., and Priest, B. V. The Occurrence and Nature of Spontaneous Arteriosclerosis and Nephritis in the Rabbit, *Arch Path* 10: 697 (Nov.) 1930

given to ten of the animals already having spontaneous nephritis to see whether further elevation in blood pressure and further disturbance in kidney function would result

Chemical and microscopic examinations of the urine were made at monthly intervals. The urine was obtained by pressure on the bladder in most instances, but occasionally animals were placed in metabolic cages and it was caught in containers

At the end of two years, and again at the conclusion of the experiment one year later, the nonprotein nitrogen, the urea nitrogen, the carbon dioxide combining power of the blood and the phthalein excretion were determined

Blood pressure determinations were made at monthly intervals. We have used the method of Van Eweyk¹³ for the past eight years. Several thousand determinations have been made with it, most of them by one of us (Miss Priest). The technic of the procedure has been so developed that we are certain very satisfactory readings are obtained. Each reading is checked one or more times and the average taken. Various other methods for taking blood pressures in rabbits are described, but in our hands none has proved so satisfactory as this one.

URINARY CHANGES

At the beginning of the experiment (Oct 1, 1925), the urine of each animal contained albumin and casts. Monthly examinations during the first year demonstrated the persistence of these abnormalities. All of the animals for months at a time had albumin and casts in their urine consistently. Occasionally the urine from one or two of them would be normal, but not longer than for two successive months.

During the second year (Jan 1, 1927, to Jan 1, 1928), the albumin increased, casts were more numerous, and normal urine was not obtained from the same animal for a period longer than one month.

Near the end of the third year twelve of the animals died, six in the alfalfa-barley group and six in the liver group, leaving four survivors in each group at the conclusion of the experiment on Jan 1, 1929. At necropsy pneumonia was present in five animals, one had died from a ruptured blood vessel following the passage of a stomach tube, while in the remainder the cause of death was not apparent. Uremia might have been accountable, but uremic symptoms had not been present during life.

The exhibition of the liver diet during the year exaggerated in pronounced fashion the urinary abnormalities of the ten rabbits receiving it.

13 Van Eweyk, C, and Schmidtman, M. Zur Methodik der Blutdruckmessung beim Kaninchen, *Virchows Arch f path Anat* 236 420, 1921

Casts and albumin were consistently present in greater amounts than in the urine from the remainder of the group

That the renal changes were probably of a degenerative nature and not of inflammatory origin was evidenced by the fact that blood cells were not found in the urinary sediments

There was a substantial increase of the nitrogenous bodies in the blood in every instance, except for rabbit 78 which showed a fall in the nonprotein nitrogen from 43.5 to 40 mg, and in the urea nitrogen from 29.4 to 20.8 mg per hundred cubic centimeters (see the accompanying table). The kidneys of this animal were histologically unaltered, except for minor changes in the vessels and glomerular capsules. The phthalein

*Blood Chemistry and Phthalein Excretion of Eight Surviving Rabbits**

	Carbon Dioxide Combining Power		Nonprotein Nitrogen		Urea Nitrogen		Phthalein (1 Hour)	
	Jan., 1928	Jan., 1929	Jan., 1928	Jan., 1929	Jan., 1928	Jan., 1929	Jan., 1928	Jan., 1929
Liver rabbit 63	42.4	36.6	37.0	38.8	22.7	30.3	51	53
67	55.1	49.0	32.3	42.5	18.5	25.0	61	49
77	46.2	55.7	36.3	35.5	18.7	26.3	67	50
79	45.2	51.0	37.0	62.5	13.0	38.4	51	35
Barley rabbit 61	32.8	30.0	40.0	58.8	22.7	31.2	74	85
62	51.9	55.7	36.4	47.6	21.4	23.8	66	46
69	51.9	50.0	32.3	32.2	12.5	17.6	46	39
78	55.7	61.4	43.5	40.0	29.4	20.8	83	70
Average (liver)	47.2	48.0	35.6	54.8	18.2	30.0	57.5	46.7
Average (barley)	48.0	49.2	38.0	44.6	21.5	23.3	67.2	60.0
Average entire group	47.6	48.6	36.8	49.7	19.8	26.6	62.3	53.3

* The first four rabbits in the table belong to the liver diet group, the second four to the group fed the alfalfa-barley mixture. The figures in the left-hand column under each heading represent the determinations made at the end of the two-year period, the figures in the right-hand column, those made at the conclusion of the experiment one year later. At the bottom of the table are the average values for the two groups of four animals, and for the entire group of eight animals.

excretion was diminished in each instance, with likewise one exception. Rabbit 61 had an excretion of 74 per cent at the end of the two-year period, increasing to 85 per cent at the conclusion of the experiment, but as the blood metabolites had increased during this time and chronic nephritis was present histologically, this may have been due to a technical error.

In comparing the group fed liver with that fed alfalfa-barley, it is seen that the changes were more pronounced in the former. The average value of the nonprotein nitrogen of these four animals had increased from 35.6 to 54.8 mg, while in the other group the increase was only from 38.0 to 44.6 mg. The urea nitrogen of the liver group increased from 18.2 to 30 mg, as compared with an increase from 21.5 to 23.3 mg for the remaining animals. The decrease in the phthalein

excretion—from 57.5 to 46.7 per cent in the first group and from 67.2 to 60 per cent in the second—was also in accord¹⁴

The changes in the carbon dioxide combining power were too slight to be of significance. They are tabulated as a matter of interest.

It would seem that spontaneous renal damage in the rabbit is accompanied by retention of nitrogenous substances in the blood, and by a decrease in the phthalein excretion, and that the feeding of a liver diet serves to enhance the damage already present, as measured clinically by these changes.

BLOOD PRESSURE

As mentioned, blood pressure determinations were made monthly on each animal, every reading being checked at least once. There was a gradual increase in pressure in all of the animals, except the controls. Wide variations were at times encountered from month to month (perhaps as a result of extraneous factors, such as season, temperature, time of day, restlessness during the determination, etc.), which are reflected on the charts, but the general trend was upward. The liver diet group showed a more rapid increase and a higher terminal average pressure.

Because of the wide fluctuations, it is perhaps inaccurate to compare actual values, but the figures may be of some interest. The animals on the liver diet, with an average initial pressure of 86 mm. of mercury, showed at the conclusion of the experiment one year later a pressure of 118 mm., or an increase of 32 mm. For the same period of time, the animals not receiving liver showed an increase from 98 to 112 mm., or only 14 mm.

It appears that the elevation of blood pressure in our animals was roughly proportional to the degree of the urinary changes, to the blood chemistry alterations and to the decrease in phthalein excretion. That renal (and arterial) injury is reflected to a certain extent in the height of the blood pressure in man seems fairly certain. Allbutt¹⁵ has said that the pressure rises in every case of primary contracted kidney and in most cases of secondary contraction wherein the glomeruli are widely affected. By analogy, we might expect the same phenomenon in the rabbit, and our results indicate such a possibility. At any rate, the conclusion is justified that spontaneous nephritis in the rabbit, if of suffi-

14 It may be argued that the differences in these figures are not statistically significant, as the values do not lie well outside the standard deviation of the mean. Since, however, the other elements of the study tend in the same direction, namely as indicating a more severe renal lesion in the liver diet group, the differences are suggestive.

15 Allbutt, T. C. *Arteriosclerosis*, New York, The Macmillan Company, 1925, p. 13.

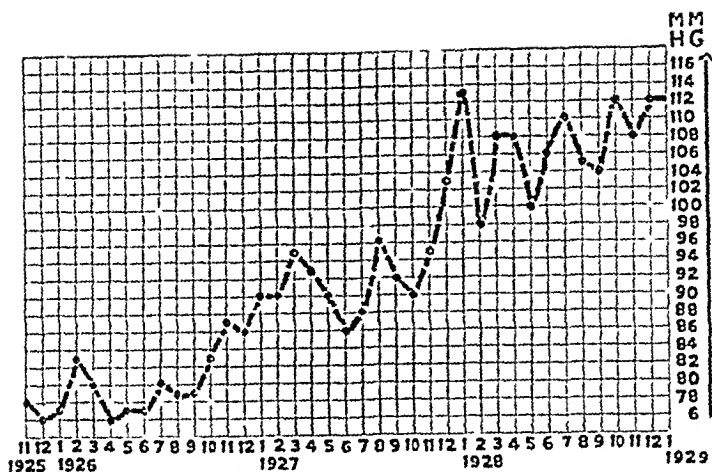


Chart 1—The blood pressure range for all the animals for the entire thirty-six months, with the exception, during the last year, of those fed the liver diet. Each reading on the chart expresses the average of all determinations made at that particular time.

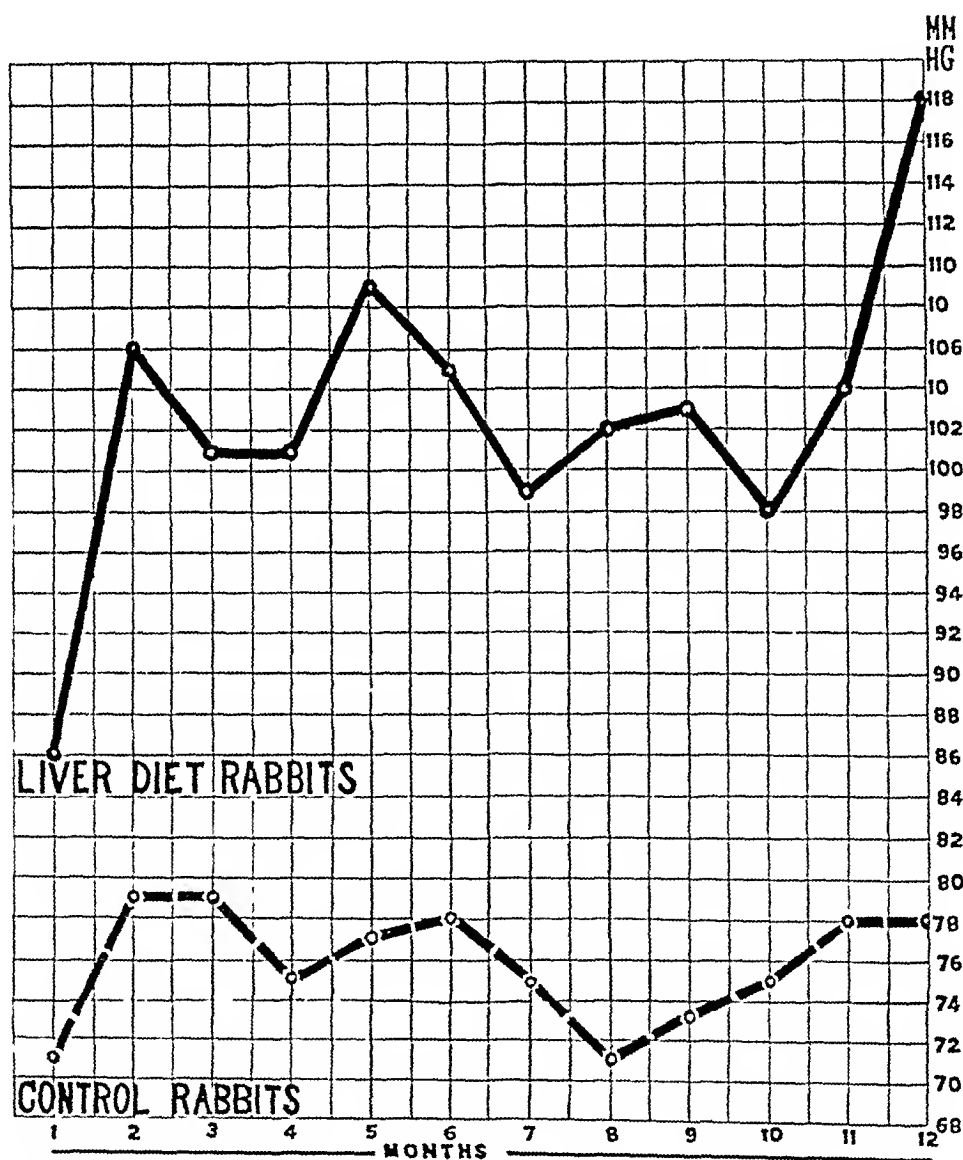


Chart 2—Blood pressure range of ten rabbits with spontaneous nephritis fed a high liver diet for one year compared with that of twelve control animals.

cient degree to be recognized clinically, is accompanied by an elevation in blood pressure not encountered in normal rabbits. The feeding of a high protein (liver) diet causes a further increase in pressure.

SUMMARY

1 Spontaneous nephritis in the rabbit, pathologically of a diffuse type and indistinguishable from that experimentally produced, occurred in approximately 8 per cent of supposedly normal animals.

2 It was evidenced in the living animal by the persistent presence of albumin and casts in the urine, retention of nitrogen bodies in the blood, decrease in phthalein excretion and elevation of blood pressure. These manifestations were roughly proportional to one another and to the degree of renal injury.

3 The exhibition of a high protein (liver) diet, given over a period of one year to animals that for two years previously had had a well marked spontaneous chronic nephritis, exaggerated the foregoing manifestations.

4 Experimentally fed high protein diets increased preexistent renal damage.

DIAGNOSIS OF SYPHILITIC AORTITIS UNCOMPLICATED BY AORTIC REGURGITATION OR ANEURYSM

COMPARISON OF CLINICAL AND NECROPSY OBSERVATIONS IN
ONE HUNDRED AND FIVE PATIENTS

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The early diagnosis of syphilitic aortitis, before the development of aortic regurgitation or aneurysm, is a question of fundamental importance in the treatment of cardiovascular syphilis. When the aortic valves have been so distorted as to produce incompetency or when the wall of the aorta has weakened to the point of producing saccular dilatation, the utmost to be expected of treatment is some degree of symptomatic relief and the possible prolongation of life to more than the usual span of about two years from the appearance of symptoms¹. If, however, involvement of the aorta can be recognized before these anatomic disasters have occurred and if appropriate treatment is instituted, it is reasonable to hope for symptomatic relief in a higher proportion of cases and prolongation of useful life for a much longer period of time.

That the problem is deserving of careful study is indicated by the gradually increasing death rate from organic heart disease, by the actuarial estimates that 2 per cent of the total population of the United States are suffering from the conditions grouped under this classification and that the annual quota of deaths from this cause now approximates 200,000,² and from the frequency with which syphilis causes heart dis-

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital

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1 Moore, J E, and Dangler, J H. The Treatment of Cardiovascular Syphilis. A Study of the Duration of Life in Forty-One Treated and Untreated Patients with Regurgitation and Aneurysm, *Am Heart J* 6 148, 1930

2 Dublin, L I. Statistical Aspects of the Problem of Organic Heart Disease, *Am Heart J* 1 359 1926

ease In New York, an analysis of 1,001 cases of heart disease indicated that about one tenth of these cases were syphilitic ³ In Baltimore, with a larger Negro population, Carter and Baker ⁴ have recently found that 15.1 per cent of 3,223 cases of heart disease in the wards of the Johns Hopkins Hospital were due to syphilis With these estimates as a base line, it is easy to arrive at the conclusion that there must be, at any one time, about 240,000 persons in the United States with definite cardiovascular syphilis, of whom more than 20,000 die each year In the light of the present state of diagnostic acumen, it would seem that the vast majority of these afflicted persons have already passed through the stage of simple aortitis to aortic insufficiency or aneurysm

TABLE 1—*The Incidence of Cardiovascular Syphilis Among Ten Thousand Syphilitic Patients (of Whom Six Thousand Four Hundred and Twenty had Late Syphilis [Turner])*

		Aortitis	Aortic Insufficiency	Angina Pectoris	Aneurysm	Other	Percentage of Total Late Cases with Cardiac Involvement
White	Male	51	37	8	17	2	8.7
	Female	19	11	1	3	4	4.8
Negro	Male	144	86	5	51	20	17.9
	Female	118	40	3	18	11	7.2
Percentage of late syphilis, showing various types of cardiovascular involvement		5.1	2.7	0.2	1.2	0.5	

ESTIMATES OF THE FREQUENCY OF SYPHILITIC AORTITIS

The frequency of aortic syphilis may also be estimated from the standpoint of its clinical incidence in a large population of syphilitic patients or of the frequency with which it is discovered at necropsy on syphilitic persons Turner ⁵ has published data bearing on the former point, based on the admission diagnoses of 10,000 syphilitic patients in this clinic His figures, reproduced in table 1, show the usual predominance of cardiovascular syphilis in Negroes as compared to white persons, and in males as opposed to females They also indicate that in a syphilis clinic for ambulatory patients, the diagnosis of syphilitic aortitis, uncomplicated by aortic regurgitation or aneurysm, has been

3 Wyckoff, J, and Lingg, C Statistical Studies Bearing on Problems in the Classification of Heart Diseases II Etiology in Organic Heart Disease, Am Heart J 1 446, 1926

4 Carter, E P, and Baker, B M, Jr Certain Aspects of Syphilitic Cardiac Disease, Bull Johns Hopkins Hosp 48 315 (May) 1931

5 Turner, T B The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases Bull Johns Hopkins Hosp 46 159 1930

made as frequently as that of all other types of syphilitic heart disease. To what extent this diagnosis is justifiable is the part of the present and a subsequent study to discover.

As to the incidence of aortitis in syphilitic patients at necropsy, there are widely divergent estimates, apparently depending on the minuteness with which pathologic studies are made. In Germany, on the basis of 23,105 necropsies from the Rudolf Virchow Krankenhaus, Langer⁶ maintained that from 70 to 80 per cent of all syphilitic patients show anatomic evidence of involvement of the aorta (simple aortitis, aortic regurgitation or aneurysm). We reproduce here two charts based on Langer's material, the first of which shows the incidence of syphilitic aortitis by years, the second, its incidence among syphilitic persons in

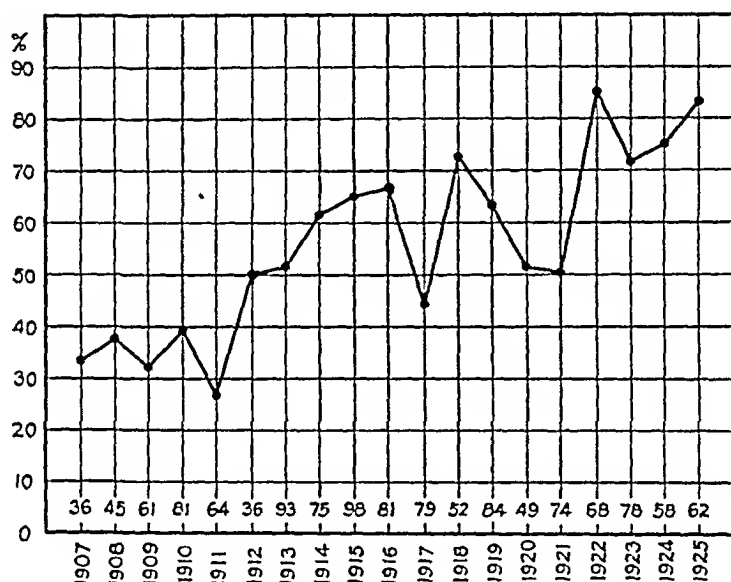


Chart 1—Curve to show the percentage incidence of syphilitic aortitis in autopsies on syphilitic patients. The figures on the base line show the number of cases of syphilis found at necropsy. Based on 23,105 necropsies from the Rudolf Virchow Krankenhaus (Langer, E. *Munchen med Wchnschr* 73: 1782, 1926). Aortitis was diagnosed ante mortem in 284 cases, or 39.3 per cent; it was not diagnosed ante mortem in 437 cases, or 60.7 per cent.

different age groups. Langer pointed out that of the 721 cases of syphilitic aortitis found at necropsy, only 284, or 39.3 per cent, were diagnosed during life. The sharp increase in the incidence of aortitis beginning in 1912 and continuing thereafter is attributed by Langer (and by others in Germany, on the basis of similar studies) to the influence of the introduction of arsphenamine into the treatment of syphilis. It seems equally possible to explain it, however, on the basis of more

⁶ Langer, E. Die Häufigkeit derluetischen Organveränderungen insbesondere der Aortitis luetica, *Munchen med Wchnschr* 73: 1782, 1926.

accurate pathologic study with increasing knowledge of the microscopic appearance of aortic syphilis

In this country, Warthin has been constantly insistent on the importance of syphilis of the aorta. His most recent figures report ⁷ gross or microscopic evidence of syphilis (more usually the latter) in 90 per cent of 490 autopsies on syphilitic patients over 25 years of age. Incidentally the percentage incidence of aortitis in syphilitic adults reported by him for the decade from 1909 to 1919 is 97.6, and for the decade from 1919 to 1929, 86.3, lending weight to the opinion that added pathologic experience and not the effect of arsphenamine is the factor responsible for the increased incidence in Langer's material.

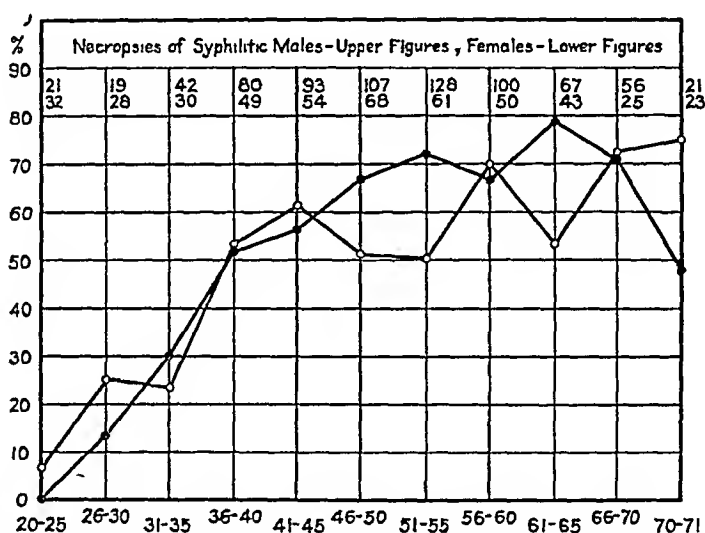


Chart 2—Percentage incidence of syphilitic aortitis among syphilitic patients at different age groups—necropsy data from Langer

It is probably true, therefore, that invasion of the aorta by the *Treponema* is as universal in syphilitic infection as is invasion of the nervous system. Every syphilitic patient is a potential candidate for the development of cardiovascular syphilis. It is necessary to distinguish, however, between invasion and involvement of the aorta, in the same sense as we have come to distinguish between invasion of the nervous system and tissue involvement extensive enough to produce the clinical picture of neurosyphilis. One can hardly expect of any clinician sufficient expertness in diagnosis to enable him to detect the presence of a single microscopic focus of round and plasma cell infiltration in the aortic wall. Unfortunately, Warthin, who has done the most careful work in the pathology of syphilis, has published no data indicating the

⁷ Warthin, A. S. The Lesions of Latent Syphilis, *South M J* 24:273, 1931

proportion of cases in which the pathologic lesions were so insignificant as to be incapable of producing symptoms or physical signs, as compared with those in which the lesion was so extensive as to have resulted in actual clinical disease. Adequate studies from other pathologists are also lacking, since few have devoted as much attention as Warthin to the minutiae of microscopic pathologic diagnosis in syphilis.

From the clinical standpoint, there are wide differences of opinion as to the possibility of arriving at an accurate diagnosis of syphilitic aortitis in the absence of aortic regurgitation or aneurysm. At the present time, the consensus among internists probably favors the group which holds that, in view of the frequency of arteriosclerotic changes in the aortas of many persons, syphilitic or otherwise, after the age of 50, such a diagnosis cannot be safely made.⁸ This opinion is, of course, based on the fact that syphilitic aortitis is often found at necropsy when unsuspected during life, and conversely that it has sometimes been absent at necropsy when all the so-called classic symptoms and signs both physical and roentgenologic, were present during life.

THE POSSIBILITY OF CLINICAL DIAGNOSIS OF UNCOMPLICATED AORTITIS

It occurred to us that information of value as to the possibility of accurate clinical diagnosis of uncomplicated aortitis might be obtained by an approach from two angles: (1) a comparison of the clinical with the necropsy observations in those patients in whom syphilitic aortitis was discovered at necropsy, whether or not recognized in life, and (2) a survey of the clinical outcome, for evidence of progression to valvular incompetency or aneurysm or, when possible, to the autopsy table, in a series of patients in whom the diagnosis was made during life. The present article describes the results of a study of the first group of patients.

The records of the department of pathology of the Johns Hopkins Hospital from 1910 to 1930 were reviewed. All cases with aortic regurgitation or aortic aneurysm were excluded from consideration, as were likewise certain instances in which the presence of extensive aortic arteriosclerosis rendered doubtful the pathologic diagnosis. After these exclusions there remained 105 cases with definite uncomplicated syphilitic aortitis, in all of which the pathologic diagnosis was made on the basis of grossly visible lesions of syphilis in the aorta, confirmed in 84 by microscopic examination. The clinical records of these patients were then studied, in order to determine the frequency with which the diagnosis was accurately made during life.

⁸ Conner, L. A. in discussion on Steel, D. *Am Heart J* 6:65, 1930.

Before proceeding to a discussion of the results it is necessary to consider the obvious criticism that the pathologic diagnosis of syphilitic aortitis was sometimes or often erroneous, and that therefore conclusions drawn from such material are untrustworthy. To this, one can reply only that the gross and histologic tissue examinations were made over a twenty year period by many members of the staff of the department of pathology, and that in most instances both gross and microscopic specimens were also reviewed by a senior member of the staff. Furthermore, the pathologic picture of syphilitic aortitis is quite characteristic, and, except in the presence of extensive aortic atherosclerosis, is not easily confused with other changes. In most of the instances here reported there was confirmatory clinical or pathologic evidence of syphilis. Unfortunately, specimens have not been preserved as a routine measure, so that we were unable to examine personally the aortas in question.

TABLE 2—*A Comparison of the Correctness of the Clinical and Pathologic Diagnosis of Syphilitic Aortitis in One Hundred and Five Cases so Diagnosed at Necropsy*

	Total Cases	Syphilitic Aortitis		Diagnosis Could Have Been Suspected on Basis of			Diagnosis Obscured by Other Cardiovascular Lesions	Heart and Aorta Thought Clinically Normal	Patient Too Ill for Adequate Examination
		Definitely Diagnosed	Suspected	Physical Signs	Symptoms	Both			
Medical service	63	4	12	12	2	9	9	11	4
Surgical service	43		1	5	4	3	3	23	3
Total	105	4	13	17	6	12	12	34	7
Percentage of total		16.2		33.3			11.4	32.3	

The 105 patients in this series entered the hospital for a wide variety of causes. Their histories were taken and the first physical examination made by an intern, in most instances, the physical examination was repeated once or several times by senior members of the resident staff and by visiting consultants. Naturally, the twenty year period covered by the study necessitates the use of records made by many physicians of varying degrees of clinical proficiency and with greater or less special interest in cardiovascular disease or in syphilis. In many instances, the acuteness of the final illness prevented careful history taking, or its character prevented accurate physical examination of the heart and the aorta. Many records, therefore, fail to include either positive or negative statements as to the presence or absence of suggestive signs or symptoms. In such cases, we have recorded "no data available" and have attempted to keep these limitations in mind throughout the study. In one sense however, this is less of a drawback for our purposes than might be anticipated. We may fairly consider these clinical records to represent the average of intelligent medical practice of the past twenty years.

The results of this survey are summarized in table 2. Sixty-three patients died in the medical wards of the hospital, 42 were in such various surgical services as obstetrics, gynecology, urology and general surgery. The diagnosis of syphilitic aortitis was correctly made before death in 4 instances, or 3.8 per cent. In an additional 13 patients, one or more of the several examiners had suspected that there was something wrong with the patient's aorta and had recorded an impression diagnosis of dilated aortic arch, aneurysm or aortic regurgitation, but in none of these instances was the impression taken sufficiently seriously as to be included in the final diagnosis. However, including these 13 patients as clinical successes, the diagnosis was correctly made or suspected in only 16.2 per cent of the group. All but 1 case were recognized on the medical service, and even in the one exception, the suspicion of syphilitic aortitis was raised by a consulting internist.

In all the cases correctly diagnosed or suspected, either the usual symptoms of substernal pain, dyspnea on exertion or paroxysmal nocturnal dyspnea or the classic physical signs of widened retromammary dulness, pulsation in the suprasternal notch, an aortic systolic murmur or an altered tympanic bell-like quality of the aortic second sound, or both symptoms and signs together, were present. These symptoms and signs, however, were also present to some degree in an additional 35 patients, or 33.3 per cent of the series, in whom their significance was completely disregarded by all examiners. In these patients the question of syphilitic involvement of the aorta was not mentioned in impression or in final diagnosis, though it is certainly fair to say that a higher index of suspicion on the part of the various examiners and consultants should have prompted some consideration of the possibility. In 17 of these patients, physical signs were present without symptoms, in 6 instances suggestive symptoms (usually antedating the symptoms of the final illness) occurred in the absence of physical signs, and in 12 patients, even the association of signs and symptoms was overlooked.

In the remaining 53 patients, the diagnosis of syphilitic aortitis apparently could not have been made. Seven of these were moribund on admission to the hospital and there was no opportunity for careful history taking or examination of the heart. In 12 the symptoms and signs of aortitis were obscured by some other cardiovascular condition such as hypertensive cardiovascular disease, rheumatic heart disease with auricular fibrillation, bacterial endocarditis, adherent pericardium, etc. Thirty-four patients, 11 medical and 23 surgical, died with no suspicion in the mind of any examiner that there was anything at all the matter with the heart or aorta. Whether this is because all suggestive symptoms and signs were actually absent or because their presence was overlooked by inadequate or careless history taking or physical examination cannot be determined.

It is true, however, that the majority of these patients were admitted to the hospital for an acute illness unrelated to syphilis or heart disease, that attention was thus directed away from the heart, and that in many patients on the surgical services examination was not made by an experienced internist. It will presently be shown that, judging by the extent of the pathologic change found at necropsy, clinical diagnosis was not necessarily impossible in this last group of patients. Even assuming that it was impossible, we arrive, however, at the startling conclusion that of the total number of 105 patients, a correct antemortem diagnosis was made in 4 and suspected in 13, while it might have been made in 52, had the signs and symptoms actually present been correctly interpreted.

TABLE 3—*Race and Sex Distribution and Age at Death of One Hundred and Five Patients with Syphilitic Aortitis*

		Total Cases	Age at Death				
			21 30	31 40	41 50	51 60	61+
White	Male	26		8	9	4	5
	Female	5	2		1	2	
Negro	Male	53	5	12	24	6	6
	Female	19	2	12	3		2
Total			9	32	37	12	13

TABLE 4—*The Correctness of the Clinical Diagnosis of Syphilitic Aortitis as Influenced by the Cause of the Fatal Illness*

	Total Cases	Diagnosis Correctly Made or Suspected	Diagnosis Might Have Been Made	Diagnosis Obscured by Other Cardiac Findings	Diagnosis Missed (Impossible to Make?)
Fatal illness related to syphilis	24	6 (25%)	7 (29%)	5 (20%)	6 (24%)
Fatal illness unrelated to syphilis which, if diagnosed, was an incidental finding	81	10 (12%)	29 (35%)	7 (8%)	35 (43%)

The race and sex distribution and the age at death of this group of patients are shown in table 3. The usual preponderance of Negroes and of males is obvious. The fact that death occurred before the age of 51 in 75 per cent of the group is a partial answer to the question of the difficulty of differential diagnosis between syphilitic aortitis and aortic arteriosclerosis. Atherosclerosis of the aorta in these younger patients was rare, and, when present, was not often extensive.

The fatal illness that brought the patients to the hospital was in some way related to syphilis in 24 instances. These were patients with, for example, tabes dorsalis and infected urinary tracts, arsphenamine poisoning, syphilis of the liver, cardiac failure secondary to syphilitic aortitis, etc. In 81 patients the final illness had nothing to do with syphilis, which if diagnosed was entirely an incidental finding. Here

the clinical diagnoses and the primary causes of death include such widely divergent conditions as lobar pneumonia, typhoid fever, septicemia, carcinoma, postoperative peritonitis or ileus, strangulated hernia, etc. That a high index of suspicion aids in the recognition of syphilitic aortitis is indicated by the relative success of clinical diagnosis in the two groups. In only 6, or 24 per cent, of the patients whose illness was directly related to syphilis were the heart and aorta regarded as normal, while this situation existed in 35, or 43 per cent, of those in whom syphilis was only a relatively unimportant incident of the fatal illness.

From the clinical standpoint, a most difficult differential diagnostic decision is between syphilitic aortitis and hypertension. Both may produce substernal discomfort, dyspnea on exertion, widening of the aorta and a change in the intensity of the aortic second sound. Paroxysmal nocturnal dyspnea is, however, a frequent feature of syphilitic aortitis, especially with aortic regurgitation, but is uncommon in hypertension.

TABLE 5—*The Correctness of the Clinical Diagnosis of Syphilitic Aortitis as Influenced by the Presence or Absence of Hypertension*

	Total Cases	Diagnosis Made or Suspected	Diagnosis Could Have Been Made	Diagnosis Obscured by Other Cardiac Lesions	Diagnosis Missed (Impossible to Make)
Hypertension present	30	8 (26%)	10 (33%)	4 (13%)	8 (26%)
Hypertension absent	75	9 (12%)	25 (33%)	9 (12%)	32 (42%)

without left ventricular failure, many experienced examiners believe that while accentuation of the aortic second sound is common to the two groups, a tympanitic bell-like alteration of its quality is peculiar to and characteristic of syphilitic aortitis (Carter and Baker⁴). Analysis of this material indicates, as has already been repeatedly pointed out, that hypertension is not a frequent accompaniment of syphilitic aortitis, and that when present it usually depends on some other definite cause, such as chronic nephritis or arteriolar sclerosis. Since all patients with aortic regurgitation have been excluded from this study, systolic elevation of the blood pressure to 150 mm or over has been taken as a criterion of arterial hypertension. On this basis the blood pressure was normal in 75 patients, the systolic blood pressure ranged between 150 and 200 in 23, and was over 200 in 7. Curiously enough, in spite of the confusion with which every clinician is faced in the individual case, the diagnosis of syphilitic aortitis was correctly made more often in the group with than in that without hypertension and it was completely overlooked, the heart and aorta being regarded as normal much less frequently than when hypertension was absent. Perhaps this is because the existence of arterial hypertension focused attention on

the cardiovascular apparatus which otherwise was devoted to clinical abnormalities unrelated to syphilis or hypertension. At any rate, the clinician's diagnostic difficulties were actually less, instead of greater, if the aortitis was complicated by elevation of the blood pressure.

The association of other clinical or pathologic evidence of syphilis with aortitis was of incidental interest to this study. A Wassermann test of the blood was done in 81 of the 105 patients, and was found to be positive in 61, or 75.3 per cent, and negative in 20, or 24.7 per cent. Of the 20 patients with negative Wassermann reactions of the blood, 2 showed some other clinical evidence of syphilis, and 3 more gave a definite history of infection. In 14 of the 20, there was nothing whatever to suggest syphilis either clinically or pathologically except the syphilitic aortitis, though in no instance was the pathologic study (especially microscopic) so detailed as that carried out by Warthin. From the purely pathologic standpoint, aortitis with its associated secondary cardiac changes of hypertrophy, chronic fibrous myocarditis, etc., was

TABLE 6—*The Correctness of the Clinical Diagnosis of Syphilitic Aortitis as Influenced by the Extent of Pathologic Damage*

Degree of Pathologic Change	Total Cases	Diagnosis Correctly Made or Suggested	Diagnosis Might Have Been Made	Diagnosis Obscured by Other Cardiac Findings	Diagnosis Missed (Impossible to Make?)
Slight	29	3 (13%)	10 (43%)		10 (43%)
Moderate	29	4 (14%)	9 (31%)	4 (14%)	12 (41%)
Extensive	49	10 (20%)	16 (32%)	8 (16%)	15 (30%)

the only anatomic evidence of syphilis in 61 (nervous system usually not examined at necropsy), while in 44 there was associated pathologic evidence of syphilis, involving the liver in 14 patients, the central nervous system in 15, the testis in 7 and other organs in 11.

An attempt was made to estimate the degree of syphilitic involvement of the aorta from the pathologic standpoint, and to compare this with the accuracy of clinical diagnosis. While this was not always possible, because of inadequate pathologic description, nevertheless, a division into three groups on the basis of slight, moderate and extensive involvement, was attempted. Slight involvement includes those cases in which there were a few or many discrete patches of syphilitic inflammatory tissue in the aortic wall without much loss of elasticity. Extensive involvement indicates widespread, confluent infiltration with or without intimal ulceration and with marked loss of elasticity and wide dilatation (not aneurysmal) of the aortic wall. Moderate involvement includes cases intermediate between these two. As one might expect, clinical accuracy in diagnosis increases in proportion to the degree of pathologic change present. It is surprising to note, however, that symptoms, signs

or both, which made the clinical diagnosis permissible, were present in 13 of 23 patients with slight pathologic involvement (56 per cent), while these same clinical abnormalities were noted to be present in only 26, or 52 per cent, of those with extensive pathologic changes. The heart and aorta were regarded as clinically normal in 30 per cent of those with extensive aortitis. In some cases, at least, this must have depended on inaccurate clinical observation, as in the patient whose pathologic note read "huge fusiform dilation of the aorta," but in whom nothing abnormal was found in the heart or aorta before death.

It seems to us interesting and important that the x-ray was so infrequently used as a diagnostic aid in this group of patients. In only 29 patients in the entire group was a roentgenographic examination carried out. In 25 of these there was definite roentgen evidence of dilatation of the aorta. We have personally examined these plates, in some instances our interpretation had been confirmed earlier by fluoroscopy carried out by a roentgenologist. There have been numerous studies made on the roentgenologic diagnosis of syphilitic aortitis, one of the most recent of which (Steel⁹) concluded that the lesion can be suspected when (1) a diffuse dilatation is present and is associated with a normal heart silhouette, or (2) a dense, high aorta is present in a young person without previous hypertension. Obviously, teleoroentgenographic and fluoroscopic examinations should be made in every syphilitic patient with symptoms or signs suggesting aortic involvement, and many cases of probable aortitis without symptoms or definite physical signs would be detected if this examination were routine in every patient with late syphilis.

THE CRITERIA OF DIAGNOSIS OF UNCOMPLICATED SYPHILITIC AORTITIS

Carter and Baker,⁴ while they did not emphasize the question of uncomplicated syphilitic aortitis, expressed the belief that the diagnosis of cardiovascular syphilis is permissible if any five of the following seven criteria are clinically demonstrable:

- 1 The history of a relatively abrupt and unexpected onset of the symptoms of circulatory embarrassment
- 2 The presence of a positive Wassermann reaction
- 3 A demonstrable increase in the retromamillary dulness in the second interspace, and a change in the tonal quality of the aortic second sound. The fluoroscopic evidence of aortic dilatation
- 4 An absence of the signs of mitral disease, connoting rheumatic infection
- 5 The history of paroxysmal dyspnea, often nocturnal
- 6 The history of pain, particularly paroxysmal pain
- 7 Progressive cardiac failure

9 Steel, D. The Roentgenographic Diagnosis of Syphilitic Aortitis in a Review of Forty Proved Cases. *Am Heart J* 6:59, 1930.

We have analyzed our 105 cases for the incidence of these various signs and symptoms, with the result shown in table 7. These data indicate that the most consistently positive finding is roentgen evidence of aortic dilatation, and this even without the aid of fluoroscopy, from which additional information of value as to the elasticity of the aortic wall may be gathered. Next in importance is a history of symptoms of circulatory embarrassment, usually dyspnea on exertion, which in this series was more often insidious than abrupt in onset. Increased retrosternal dulness occurred in almost half the patients, one suspects from the roentgen evidence that more careful physical examination would have shown its presence in a still higher proportion. The presence of a tympanic accentuated second aortic sound was noted in only 25.8 per cent, though here, too, one is relatively certain that had a single experienced examiner been able to see all these patients, the incidence of this abnormality would have been much greater. The interpretation of this

TABLE 7—*The Incidence of Various Symptoms and Signs in Patients with Syphilitic Aortitis Proved at Necropsy*

	Total Cases with Information Available	Number of Patients Showing Symptom or Sign	Percentage
History of circulatory embarrassment	88	44	50.0
Widened retrosternal dulness	89	44	49.4
Accentuated tympanic A ₂	89	23	25.8
Roentgen evidence of widened aorta	29	25	86.0
Paroxysmal dyspnea	90	7	7.7
Pain	89	16	17.9
Cardiac failure (not terminal)	92	24	26.0

change in quality of the heart depends on experience. Paroxysmal dyspnea and substernal pain or discomfort were much less frequent than we had anticipated.¹⁰

Twenty-two patients in this series showed none of the symptoms or physical signs named. Thirty-three more had one or two symptoms, signs or both, while in the remainder in whom the data were available, from three to six of the criteria listed were present (not including Carter and Baker's second and fourth criteria, namely, the presence of a positive Wassermann reaction of the blood and the absence of mitral disease).

On this basis, we should tabulate, in order of relative importance, the following diagnostic criteria of uncomplicated syphilitic aortitis:

1. Teleroentgenographic and fluoroscopic evidence of aortic dilatation
2. Increased retromanubrial dulness
3. A history of circulatory embarrassment

10. Additional suggestive physical evidences of syphilitic aortitis are (1) a visible and palpable pulsation in the suprasternal notch in the absence of hypertension, and (2) a rough systolic murmur loudest at the aortic area but often also audible at the apex.

- 4 A tympanic, bell-like, tambour accentuation of the aortic second sound
- 5 Progressive cardiac failure
- 6 Substernal pain
- 7 Paroxysmal dyspnea

We believe that in a patient with known late syphilis (whether or not the Wassermann reaction of the blood is positive), the presence of any three of these criteria is strong evidence for the diagnosis of syphilitic aortitis, while the presence of any two of them renders the diagnosis probable. In a patient with a negative Wassermann reaction of the blood, with no history or other physical evidence of syphilis and without obvious disease of the mitral valve, the presence of any four of these symptoms or signs is also clinical justification for the diagnosis.

This position will, we hope, be materially strengthened by the corollary of the present study. In contrast to following, as we have done, the patient with syphilitic aortitis backward from the necropsy table through his clinical course, we must next follow a group of patients in whom the diagnosis was actually made during life to the necropsy table when possible, to see to what extent our clinical assumptions are justified. Such a study will form the subject of a subsequent paper of this series.

We believe, on the basis of this study, that it is possible to make the diagnosis of syphilitic aortitis in the absence of aortic insufficiency or aneurysm. The percentage of correct diagnoses will increase if the physician remembers that aortitis is a frequent pathologic finding in late syphilis, if he makes specific inquiry for possible symptoms, if he looks for the common physical signs, and, above all, if he uses teleoroentgenologic examination as a routine measure in patients who have had syphilis for ten or more years.

We think that in the light of present knowledge it is fair to take the attitude that it is better for the patient, so far as the management and treatment of his syphilitic infection are concerned, to diagnose syphilitic aortitis on the basis of relatively slight suspicion during life, even if the lesion is not found at autopsy, than to fail to recognize it during life only to have it discovered at autopsy. Under the former circumstances, appropriate treatment and years of subsequent observation may well prevent the appearance of aortic insufficiency or aneurysm and preserve the patient for a long and useful life. Under the latter, we shall be too often chagrined by the pathologist's announcement that the patient died of syphilitic heart disease unsuspected clinically or of the unfortunate effects of too strenuous treatment which would not have been given had the true situation been known.

SUMMARY AND CONCLUSIONS

- 1 The early diagnosis of uncomplicated syphilitic aortitis is of fundamental importance for the treatment of cardiovascular syphilis.

2 The literature indicates that deaths from organic heart disease are increasing and that syphilis is responsible for from 10 to 15 per cent of all cases grouped under this heading

3 In this clinic about 10 per cent of all patients with late syphilis show clinical evidence of cardiovascular syphilis

4 Necropsy evidence, from this country and abroad, indicates that from 80 to 90 per cent of all adults with late syphilis show pathologic evidence of syphilis of the aorta

5 In the 20 year period from 1910 to 1930, there came to necropsy in the Johns Hopkins Hospital 105 patients with uncomplicated syphilitic aortitis (without aortic regurgitation or aneurysm)

6 Sixty-three of these patients died while in the medical service, 42 were in various surgical services

7 The clinical diagnosis of syphilitic aortitis was correctly made during life in 4 of the 105 patients, in 13 more, it was suspected that something was wrong with the aorta

8 On the basis of the symptoms and physical signs recorded, the diagnosis might have been correctly made in 35 additional patients

9 In 12 instances, the diagnosis was obscured by some other form of cardiovascular disease

10 Thirty-four patients died with hearts and aortas thought clinically to be normal

11 Syphilis was infrequently a major feature of the fatal illness. When it was, aortitis was more often diagnosed correctly than when the final illness was unrelated to syphilis

12 Hypertension was an infrequent accompaniment of syphilitic aortitis, and in spite of the confusion it created in the individual case, its presence did not prevent correct diagnoses

13 The Wassermann reaction of the blood was positive in 75 per cent of these cases, and negative in 25 per cent

14 The success or failure of clinical diagnosis is compared with the extent of pathologic change present in the aortas. Symptoms and signs permitting a diagnosis were present in about half of those who showed only relatively slight gross pathologic change

15 The criteria of diagnosis are discussed, and seven frequently found symptoms or signs listed. Of these the most important are roentgenologic evidence of aortic dilatation, increased retrosternal dullness, a history of circulatory embarrassment and a change in the tonal quality of the aortic second sound

16 In patients with proved late syphilis the presence of any three of the seven criteria listed is considered justification for the diagnosis of uncomplicated syphilitic aortitis

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

I CONTROL DIET

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A review of the literature of experimental nephritis shows that investigators have failed to produce chronic renal lesions in experimental animals comparable to those noted in man. Chemicals and toxins may cause an acute fatal condition or one from which the animal will recover, but the most promising procedure seems to lie in the removal or destruction of renal tissue.

The literature dealing with the effects of experimental renal insufficiency induced by the operative removal of kidney tissue contains conflicting conclusions and results. The reasons for many of the differences can be accounted for by the lack of controlled experimental conditions, involving the dietary regimen, the amount of kidney tissue removed, the period of experimentation and the type of animal used. Since the efforts of many investigators to produce consistently such signs as hypertension, cardiac hypertrophy, polyuria, albuminuria, etc., have been unsuccessful or only partially successful, a series of experiments was devised to study certain phases of the problem on a large number of animals.

The first work on partial nephrectomy was done by Tuffier¹. This investigator removed first one kidney and later a portion of the other. He concluded that there were no changes in the elimination of urine or urea.

After the removal of three fourths of the kidney tissue in dogs, Bradford² noted that death occurred in from one to six weeks from asthenia with great wasting. If approximately two thirds of the total

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1 Tuffier, T. *Études expérimentelles sur la chirurgie du reins*, Paris, G Steinheil, 1889, quoted by Pearce, R M. *J Exper Med* **10** 632, 1908

2 Bradford, J R. *The Results Following Partial Nephrectomy and the Influence of the Kidney Upon Metabolism*, *J Physiol* **23** 415, 1899

kidney tissue was removed, a considerable and practically permanent increase in the urinary volume was observed, but there was no appreciable change in the amount of urea excreted. The removal of three fourths of the kidney tissue was followed by a marked increase in the urinary volume accompanied by an increase in the amount of urea excreted. Under the latter circumstances, there is an increase in the nitrogenous compounds in the blood and in the tissues, particularly the muscles. No evidence of cardiac hypertrophy or of arterial change was found. Bradford suggested that the tissues of the body and particularly the muscles broke down when the kidney tissue was markedly reduced. He stated that he had no evidence to determine whether this was due to the lack of an internal secretion of the kidney. No albuminuria was noted in these experiments.

In 1905, Passler and Heinecke³ presented the first evidence of hypertension associated with cardiac hypertrophy as a result of partial nephrectomy. These investigators removed one and one-half kidneys, and at frequent intervals removed small portions of the remaining hypertrophied tissue. Of the eighteen dogs operated on, seven lived at least four weeks without cachexia after the last operation and showed the signs of renal insufficiency. Of these animals, five showed definite cardiac hypertrophy, one was close to the upper limit of normal, and one was normal. The cardiac hypertrophy was judged by comparing the weight of the left with that of the right ventricle. In the seven dogs mentioned, the ratio was 2.26 : 1 as compared to the normal of 1.76 : 1. The hypertrophy was noted only in dogs that had renal insufficiency of high degree but did not develop cachexia. The blood pressure determinations were made by cannulating the femoral artery. The increase noted varied from 15 to 29 mm. of mercury with an average of 21.5 mm. Polyuria accompanied by albuminuria and cylindruria was obtained in these animals, but no edema was noted. It is of importance to emphasize that the hypertension persisted long after the necrotic stumps had been absorbed.

Bainbridge and Beddard⁴ concluded, from their studies on cats, that the removal of three fourths of the kidney substance caused loss of appetite, wasting and death in a few days or weeks. There was an increase in nitrogen output only after the animal had lost 22 per cent or more of its body weight, which was similar to the results obtained with starving animals. The possibility of an internal secretion of the

3 Passler and Heinecke. *Versuche zur Pathologie des Morbus brightii*, Verhandl. d. deutsch. path. Gesellsch. 9: 99, 1905.

4 Bainbridge, F. A., and Beddard, A. P. The Relation of the Kidneys to Metabolism, *Proc. Roy. Soc.* 79B: 75, 1907.

kidney having any direct effect on nitrogen metabolism was excluded. They also found that there was not necessarily an increase in the volume of urine.

The work of Bainbridge and Beddard⁴ was confirmed by Pearce⁵ during the following year. No polyuria or constant albuminuria was noted.

Janeway⁶ used Carrel's⁷ method of reducing the kidney substance by ligating several branches of the renal artery. Two dogs lived for one hundred and four and one hundred and sixty-three days, respectively, and showed a moderate sustained hypertension (from 20 to 35 mm of mercury above normal) with polyuria, albuminuria and cylindruria. It was noted that the hypertension was sustained after the infarcted kidney tissue had been absorbed.

Pilcher⁸ ligated branches of the renal arteries of one dog and one cat. He made no note of the blood nitrogen level or of the blood pressure. He concluded that "with but one-fourth of the kidney substance functioning, the quantity of urine was practically normal, the urine contained no albumin or casts, cardiac hypertrophy did not occur."

Cash⁹ reduced the renal tissue of dogs by excision and by ligation of the renal vessels. A moderate increase in blood pressure was obtained shortly after the operation, provided that the portion of the kidney that was deprived of its circulation was allowed to remain *in situ*. This increased blood pressure lasted but a short time and tended to return to normal. There was no appreciable change in the blood nonprotein nitrogen or total chlorides after a reduction of from 25 to 85 per cent of the kidney tissue. No edema was noted.

Rabbits were utilized by Anderson¹⁰ in a study of renal insufficiency. He found that the operative removal of 70 per cent of the kidney tissue in rabbits does not produce hypertension even when prolonged renal insufficiency results. An increase was noted in the blood urea, which

5 Pearce, R. M. The Influence of Kidney Substance Upon Nitrogenous Metabolism, *J. Exper. Med.* **10** 632, 1908.

6 Janeway, T. C. Note on the Blood Pressure Changes Following Reduction of the Renal Arterial Circulation, *Proc. Soc. Exper. Biol. & Med.* **6** 109, 1909.

7 Carrel, A. Note on the Production of Kidney Insufficiency by Reduction of the Arterial Circulation of the Kidney, *Proc. Soc. Exper. Biol. & Med.* **6** 107, 1909.

8 Pilcher, J. B. On the Excretion of Nitrogen Subsequent to the Ligation of Successive Branches of the Renal Arteries, *J. Biol. Chem.* **14** 389, 1913.

9 Cash, J. R. A Preliminary Study of the Blood Pressure Following Reduction of Renal Substance, with a Note on Simultaneous Changes in Blood Volume and Chemistry, *Bull. Johns Hopkins Hosp.* **35** 168, 1924.

10 Anderson, H. The Relation of Blood Pressure to the Amount of Renal Tissue, *J. Exper. Med.* **39** 707, 1924, Experimental Renal Insufficiency, *Arch. Int. Med.* **37** 297 (March) 1926.

was initially greater in those that died early and was progressively increased in animals living for comparatively long periods. The specific gravity of the urine of these rabbits tended strongly toward fixation. Albuminuria and cylindruria were absent.

Allen, Scharf and Lundin¹¹ have reviewed their work on partially nephrectomized dogs, sheep and goats. These investigators found that dogs will die if more than 75 per cent of the kidney tissue is removed, but goats will survive in apparently good health with but one fifth of one kidney. In dogs on a normal diet, elevations in blood pressure of from 20 to 30 mm were obtained. These animals showed a retention of nitrogenous materials and an impaired water excretion, large volumes of administered water being retained in the blood and tissues while the urine output was scanty and the specific gravity relatively high. Marked polyuria was obtained in sheep and goats. A moderate anemia developed in these animals.

Mark¹² succeeded in producing a noticeable renal insufficiency in five dogs by ligation of the branches of the renal arteries. These animals continued in good health with no marked symptoms or loss of weight. His findings with the animals on a control diet were as follows. There was no polyuria, there was a definite loss of ability to concentrate the urine but no loss of ability to dilute it, there was a loss of ability to excrete definite amounts of ingested urea within twenty-four hours, whereas the normal dog could excrete the same amount within from two to three hours, the blood pressure remained normal.

In 1930, Mark and Geisendorfer^{12a} produced a renal insufficiency in dogs by ligation of the renal arteries and subsequent removal of the remaining kidney. They demonstrated a definite hypertension and cardiac hypertrophy in five dogs that survived the operations for an appreciable length of time. The cardiac hypertrophy was judged by microscopic measurements of the diameters of the heart fibers as well as by gross examination.

Verney,¹³ working with a perfused heart-lung double-kidney preparation, obtained an immediate increase in urinary flow after the ligation of a branch of the renal artery. The reduced kidney tissue responded

11 Allen, F M, Scharf R and Lundin, H. Clinical and Experimental Renal Deficiency, *J A M A* **85** 1698 (Nov 28) 1925.

12 Mark, R E. Untersuchungen über die Nierenfunktion. Ergebnisse partieller Nierenarterienunterbindung am Hunde, *Ztschr f exper Med* **59** 601, 1928.

12a Mark, R E, and Geisendorfer, H. Untersuchungen über die Nierenfunktion. Zur Frage des Zusammenhanges von Nierenmasse, Herzhypertrophie und Blutdrucksteigerung, *Ztschr f d ges exper Med* **74** 350, 1930.

13 Verney, E B. Experimental Reduction of Renal Tissue. *Lancet* **1** 645, 1929.

at a constant blood pressure as though it was subjected to an increased perfusion pressure. In other words, "the pressure stimulus to secretion has become more effective."

Ferris and Hynes¹⁴ removed one kidney and ligated the renal arteries of the other. A marked rise in blood pressure occurred shortly after the operation. This elevation was followed by a gradual fall ending with a base line from 10 to 15 mm. above normal.

In a preliminary report dealing with chronic renal insufficiency in dogs, Apfelbach and Jensen¹⁵ reported the results obtained after injecting particles of charcoal into the renal artery. They listed the following changes: a decrease in the ability of the kidney to concentrate and dilute urine, nitrogen retention in the blood, polyuria, a decrease in body weight and a decrease in the carbon dioxide combining power; edema and arterial hypertension did not occur. They stated that death could not be ascribed to renal insufficiency unless the foregoing syndrome occurred.

A brief summary of the results obtained after partial nephrectomy in various species will emphasize the conflicting views concerning the experimental production of arterial hypertension, renal insufficiency and cardiac hypertrophy.

1 Arterial hypertension was noted in the chronic state of renal insufficiency by Passler and Heinecke,² Janeway,⁶ Allen, Scharf and Lundin¹¹ and Maik and Geisendorfer,^{12a} hypertension in the acute stage by Cash⁹ and Ferris and Hynes¹⁴. No effect on the blood pressure was obtained by Anderson¹⁰ and by Apfelbach and Jensen.¹⁵

2 Polyuria was noted by Bradford,² Passler and Heinecke,³ Janeway,⁶ Allen, Scharf and Lundin¹¹ and Apfelbach and Jensen.¹⁵ Absence of polyuria was recorded by Bainbridge and Beddard,⁴ Pearce,⁵ Pilcher⁸ and Maik.¹²

3 Practically all workers have reported a nitrogen retention in the blood.

4 Edema was never noted in partially nephrectomized animals.

5 Albuminuria and cylindruria were not studied in any detail by any of the foregoing investigators.

14 Ferris, H. W., and Hynes, J. F. Indirect Blood Pressure Readings in Dogs. Description of Method and Report of Results, *J. Lab. & Clin. Med.* **16** 597, 1931.

15 Apfelbach, C. W., and Jensen, C. R. Experimental Renal Insufficiency in Dogs with Special Reference to Arterial Hypertension. *J. Clin. Investigation* **10** 162, 1931.

EXPERIMENTAL METHODS

A Wistar strain of the albino rat was used in this work. These animals were raised and bred in our laboratory and were free from infection and parasitic infestation. The rat is extremely well adapted to the type of work to be reported, since it is notoriously hardy and resistant to operative infection. Furthermore, large numbers of biologically standardized animals can be studied.

6 Cardiac hypertrophy was noted by Passler and Hemecke³ and Mark and Geisendorfer¹². Bradford² and Pilcher⁸ reported negative results.

The animals were anesthetized with ether, the hair over the left kidney region was clipped short, 95 per cent alcohol was poured over the area, and an incision was made directly into the peritoneal cavity. The left kidney was brought to the surface, loops of white cotton thread were placed tightly in position around both poles and then ligated off by closing the loops. By this method, from one half to three fourths of one kidney was removed from the circulation. In some cases the ligated poles were completely removed, but usually they were allowed to remain in situ. Very little hemorrhage accompanied this procedure. The ligated kidney was returned to its fossa, and the peritoneum, the muscle wall and the skin were approximated in two layers with a continuous suture of black silk. The whole procedure, including anesthesia, required from three to four minutes. One week later the right kidney was excised by a similar approach. The control animals were carried through the same operative procedure, the kidneys being exposed, handled and replaced. Other than dipping the instruments in 95 per cent alcohol before use and pouring alcohol over the skin, no aseptic precautions were taken. Following operation, there developed a few superficial abscesses, which cleared up after drainage. Neither peritonitis nor renal suppuration occurred in any animal. There was no noticeable reaction from the nonabsorbable thread used.

As a general rule, from six to eight animals of the same litter were placed in an adequately roomy cage. One control animal was allowed for every three or four nephrectomized rats. Immediately after the second operation all animals were placed on a diet containing 20 per cent dried extracted beef, 50 per cent dextrin, 16 per cent lard, 5 per cent standardized cod liver oil, 4 per cent salt mixture (Osborne and Mendel) and 5 per cent yeast. Food and water were always available.

The blood was obtained for analysis by clipping the tail of the anesthetized rat. The hemoglobin determinations were made by the Newcomer method. The Folin and Svedberg¹⁶ micromethod was used for the determination of nonprotein nitrogen. The specific gravity of the serum, whole blood and urine was measured by the falling drop method of Barbour and Hamilton¹⁷.

Twenty-four hour specimens of urine were obtained for study by placing the rats in individual metabolism cages similar to those described by Levine and Smith¹⁸. Food was withdrawn twenty-four hours before the rat was placed in the

16 Folin, O., and Svedberg, A. Micro Methods for the Determination of Non-Protein Nitrogen, Urea, Uric Acid, and Sugar in Unclotted Blood, *J Biol Chem* 88 85, 1931.

17 Barbour, H. G., and Hamilton, W. F. The Falling Drop Method for Determining Specific Gravity, *J Biol Chem* 69 625, 1926.

18 Levine, H., and Smith, A. H. A Cage Device for the Study of Ketosis and Nitrogen Metabolism on Small Animals, *J Lab & Clin Med* 11 3, 1925.

metabolism cage in order to eliminate the possible effect of food metabolites on urinary excretion. The animal was then placed in the cage without water for twenty-four hours, and the urine for this period was collected. The volume was measured, the urine centrifugated and the specific gravity and albumin¹⁹ determined.

Unfortunately no satisfactory method for following the blood pressure in the rat at frequent intervals could be devised. An attempt was made to apply the universally accepted clinical method of determining blood pressure by applying a small cuff connected with a clinical mercury manometer to the tail of the rat. The animal was anesthetized with ether, the cuff applied to the tail and the pressure increased above the expected blood pressure. The tail was cut with sharp scissors and immersed in a small beaker containing isotonic citrate solution. The pressure was then lowered until there was a marked spurt of blood from the tail artery. This point was extremely sharp in most animals. However the blood pressure obtained by this method was extremely variable and much lower than that obtained by cannulating the carotid and therefore was abandoned. In moribund animals showing a carotid blood pressure of about 100 mm of mercury, it was frequently noted that the tail blood pressure would be about 20 mm. In animals showing a high blood pressure by the carotid method, it was usually found that the tail pressure was also high.

An effort was made to cannulate the tail artery, but this method was also unsatisfactory.

All blood pressure readings to be given were obtained by cannulating the carotid just before the animal was killed. The carotid was cannulated with needles of varying bores depending on the size of the vessel. A mercury manometer of about 0.7 mm bore that was checked against a clinical manometer was used. The apparatus was similar to that used by Rous and Drury²⁰. The system was filled with a solution of 5 per cent sodium citrate to prevent clotting. The level of the mercury was adjusted to approximate the expected pressure in order to prevent loss of blood into the manometer. On separating the carotid of an hypertensive rat from the surrounding fascia, the vessel was found to be tortuous and would bulge from its normal position. The carotid arteries in these animals were markedly dilated, but no gross thickening or sclerosis was noted. Through observations of the carotid we were able by experience to estimate the blood pressure level with considerable accuracy. The animal was anesthetized with ether, the artery was isolated and cannulated, and pressure readings were begun within two minutes of the beginning of the anesthesia. Final readings were taken while there was a corneal reflex but before the animal awakened sufficiently to move.

The heart and kidney were removed immediately after death, weighed and either preserved for microscopic study²¹ or used for the determination of the total solids. Care was taken to remove all of the blood from the heart cavities. A major part of the atria was removed in order to get rid of the first portion of the aorta. The kidneys were weighed after the remaining portions of the necrotic stumps had been removed. Total solid determinations of the heart and kidneys were made by drying for twenty-four hours at from 100 to 110 C in a constant temperature oven.

¹⁹ Folin, Otto. *A Laboratory Manual of Biological Chemistry*, New York, D Appleton & Company, 1926, p 210.

²⁰ Rous, P, and Drury, D R. *Outlying Acidosis Due to Functional Ischemia*, J Exper Med **49** 435, 1929.

²¹ The histopathologic studies of the hearts and kidneys will be reported by Dr J Edwin Wood, Jr.

EXPERIMENTAL RESULTS

Stock Animals—In order to test the reliability of our standards of measurements of the heart, kidneys and blood pressure in intact animals of different ages, weights and sex, a number of stock animals²² were killed. The surface area was determined by the formula proposed by Lee²³ in which $S = 12.54 \times W^{0.60}$. The ratio of $\frac{\text{heart or kidney weight}}{\text{surface area}} \times 100$ has proved to be satisfactory in determining the relative changes in the weight of the heart or kidney, particularly of the heart. In table 1 it will be seen that the variations for the heart ratio were small, the average ratio being 0.177. The ratio for the kidneys was slightly more variable, with an average of 0.486. The limits of blood pressure in these animals ranged between 110 and 136 mm of mercury.

TABLE 1—*Stock Animals*

Rat	Weight, Gm	Heart Weight, Gm	Heart Weight	Kidney Weight, Gm	Kidney Weight	Blood Pressure, Mm Hg	Age at Death, Days
			Surface Area × 100		Surface Area × 100		
1	342	0.095	0.167	1.968	0.472		142
2	296	0.083	0.163	1.782	0.467	120	142
3	296	0.087	0.180	1.875	0.490	110	142
4	336	0.158	0.185	2.106	0.513	126	147
5	326	0.112	0.177	2.025	0.503	136	147
6	263	0.025	0.176	1.788	0.503	122	166
7	269	0.032	0.176	1.767	0.490	135	166
8	286	0.088	0.185	1.960	0.527	132	202
9	290	0.064	0.177	1.811	0.482	130	332
10	173	0.495	0.179	1.233	0.448	126	332
11	226	0.608	0.188	1.472	0.456	126	337
Average			0.177		0.486	126	

Control Animals—As previously stated, the control animals were kept from three to two hundred and twenty-four days after laparotomy under identical conditions as the partially nephrectomized rats (table 2). The blood nonprotein nitrogen fluctuated between 30 and 54 mg per hundred cubic centimeters (average, 38 mg). The specific gravity of the serum varied between 1.0250 and 1.0290 (average, 1.0270). The carotid blood pressure varied between 106 and 145 with an average of 120 mm, which closely approximated the figures obtained by Durant²⁴ in the adult white rat. Since there was but one animal the blood pressure of which exceeded 140 mm, this figure was chosen as the upper limit of normal blood pressure.

22 The animals were fed a dog food, Bal Ra prepared by the Valentine Meat Juice Company, Richmond, Va.

23 Lee M O. Determination of the Surface Area of the White Rat with Its Application of the Expression of Metabolic Results, *Am J Physiol* 89:24, 1929.

24 Durant, R R. Blood Pressure in the Rat, *Am J Physiol* 81:679, 1927.

The specific gravity of the twenty-four hour specimens of urine collected for the concentration test showed variations from 1 0352 to 1 0733 (average, 1 0600) The specific gravity of the urine of the animals having access to food and water averaged about 1 0500 The

TABLE 2—Control Animals

Rat	Weight, Gm	Duration of Experiment, Days	Age at Death, Days	Hemo globin, Gm per 100 Ce	Heart Weight		Kidney Weight	Blood Pressure, Mm	Non protein Nitrogen, Mg per 100 Ce	Twenty Four Hour Urine Concentration Test		
					Surface Area × 100	Surface Area × 100				Volume, Ce	Specific Gravity	Albumin, Gm
388	326	3	160		0 185	0 557	118		45			
335	259	4	335		0 176	0 466	110		54			
324	230	11	221		0 173	0 533			43			
311	212	12	241		0 192	0 423	120		40	3 5	1 0391	
315	267	12	153		0 169	0 432	118		40	3 7	1 0428	
426	366	72	295	15 3	0 193	0 417	124		48	1 9	1 0710	
319	400	72	269		0 180	0 438	145			2 9	1 0671	
90	183	79	389		0 183	0 427	120		36	1 3	1 0631	
573	324	87	391	15 8	0 178	0 503	116			3 5	1 0543	
570	310	87	394	16 1	0 201	0 522	116			2 4	1 0724	
545	279	97	337	16 8	0 203	0 500	110			3 7	1 0367	0 006
543	252	97	337	12 7	0 185	0 537	116		33	2 4	1 0632	
547	226	97	256	15 0	0 202	0 536	106		34	3 6	1 0456	0 003
550	267	97	245	16 6	0 207	0 520			26	3 1	1 0484	
175	301	99	153		0 187	0 454	140		43	2 8	1 0449	
575	304	100	270	12 4	0 172	0 506	108		29	2 5	1 0540	
554	207	101	283	17 3	0 168	0 398	112		50	2 3	1 0512	
477	277	109	268	10 9	0 192	0 480	110		45	3 3	1 0409	
87	192	112	398		0 187	0 380	106			1 5	1 0631	
506	214	119	191	18 1	0 165	0 408	110		42	2 0	1 0582	
442	345	122	271	15 8	0 181	0 387	130		32	2 7	1 0586	
415	380	124	284	15 0	0 192	0 294	120		31	3 9	1 0470	0 003
20	192	133	334		0 166	0 400	112		48	1 4	1 0535	
19	225	133	326		0 172	0 437	126		47	1 1	1 0673	
23	160	136	327		0 178	0 442	120		40	1 5	1 0723	0 005
75	255	140	276		0 202	0 432	116		35	1 3	1 0705	
14	286	167	234		0 183	0 443	138			2 0	1 0605	
13	296	168	235		0 190	0 498	126			3 0	1 0617	
118	284	173	222	14 8	0 187	0 432	118			1 5	1 0692	
109	181	174	223	15 0	0 188	0 386	120		30	1 4	1 0642	
110	226	174	223	12 1	0 215	0 364			30	2 1	1 0607	
111	193	174	223	13 0	0 184	0 375	114		35	0 9	1 0621	
150	418	182	395	16 0	0 166	0 368	126		23	2 7	1 0518	
94	255	183	344	16 0	0 193	0 417	134		30	0 6	1 0708	
95	204	183	344	17 0	0 185	0 414	142		33	1 6	1 0665	
8	245	185	290	15 3	0 193	0 390	110		29	2 7	1 0624	0 003
61	195	187	268	14 5	0 177	0 411	140		37	1 2	1 0793	
52	241	198	485		0 184		108			2 2	1 0617	
55	264	198	485		0 202	0 380	116			1 9	1 0606	0 001
96	248	200	415	15 2	0 184	0 417	120			2 8	1 0399	
135	302	207	246	14 8	0 205	0 455	118		33	2 5	1 0602	0 004
70	343	211	316	17 5	0 196	0 462	110		47	5 4	1 0352	0 001
61	340	212	283	18 2	0 200	0 477			43	2 0	1 0636	
41	237	212	398	16 5	0 190	0 408	120		43	2 3	1 0553	
62	281	212	283	19 0	0 170	0 364	120		48	1 7	1 0521	
35	366	213	520	15 3	0 200	0 423	136		50	4 0	1 0470	
5	232	213	495	15 8	0 200	0 437				1 7	1 0613	
6	385	219	307	16 8	0 186	0 421	112		48	1 8	1 0605	
58	332	219	307	17 3	0 204	0 465			34	2 7	1 0622	
169	251	224	294		0 180					1 7	1 0650	
108	369	224	294	14 0	0 197	0 436	110		31	2 9	1 0547	
Average				15 5	0 191	0 438	120		38	2 4	1 0579	

albino rat can and normally does excrete a more concentrated urine than man The twenty-four hour specimen of urine obtained during a concentration test varied in volume between 0 9 and 5 4 cc (average, 2 cc) As was to be expected, the specific gravity varied with the volume The normal slight trace of albumin was most always found in the urine The sediment was constantly negative for casts

The $\frac{\text{heart weight}}{\text{surface area}} \times 100$ ratio ranged between 0.164 and 0.204 (average, 0.191). The kidney ratios were more variable. Total solid determinations of both the heart and the kidneys were almost constant, the former approximating 23 per cent and the latter 25 per cent.

An appreciable number of the control animals exhibited multiple lung abscesses, atelectasis or emphysema. In these there was a constant increase in the heart ratio, some reaching 0.250, but the blood pressure tended to be slightly lower (from 100 to 124, average, 113 in eleven rats) than in the healthy control animals. Therefore, animals with pulmonary disease were excluded.

Urinary and blood studies at frequent intervals showed that the results for an individual rat were fairly uniform over a considerable period of time. A typical case is shown in table 3.

TABLE 3—*Protocol of Rat 41, Used as Control*

Time After Operation, Days	Weight, Gm	Nonprotein Nitrogen, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Urine (24 Hour Specimen)		
				Volume, Cc	Specific Gravity	Albumin, Gm
0	240					
18		40				
29	246					
42	250	38				
58				2.1	1.0626	0.002
112	277	37				
118				2.5	1.0426	
172				2.4	1.0462	0.001
176	275	33	17.3			
211				2.3	1.0553	
212	277	41	16.5			

Notes: Rat 41, male, aged 183 days. Killed April 16, 1931. Not sick, no pathologic changes. Blood pressure 120, heart ratio 0.190, total solids 22.9 per cent, kidney ratio 0.403, total solids 25.0 per cent, serum specific gravity 1.0270, specific gravity of whole blood 1.0627, microscopically, urine negative.

The Early Postoperative Stage in Apparently Well, Partially Nephrectomized Animals—Definite nitrogen retention and pronounced polyuria were noted during the first few days after the second operation. Within two weeks, however, there was usually a decreased volume of urine. About the third week, the degree of renal damage apparently determined whether the nitrogen retention and polyuria were to be decreased or increased. The loss of weight noted in these animals was probably due for the most part to the frequent concentration tests made. Table 4 contains the details of changes in representative animals during the early postoperative stage.

These rats showed no signs of listlessness, emaciation or ruffled hair and as far as could be determined by observation, were in relatively good condition, apparently they might have lived for from one to six months. A number of rats showing a marked renal insufficiency, as

judged by the concentration test, were killed at various periods shortly after the second operation in order to study the blood pressure changes and the heart and kidney weights during this stage (table 5). A marked renal insufficiency accompanied by varying degrees of nitrogen retention was characteristic. Renal hypertrophy was noticeable after the second week. The degree of albuminuria did not differ appreciably

TABLE 4—*Protocol of Rats 606, 585 and 603*

Time After Operation, Days	Weight, Gm	Nonprotein Nitrogen, Mg per 100 Ce	Hemoglobin, Gm per 100 Ce	Urine (24 Hour Specimen)		
				Volume, Ce	Specific Gravity	Albumin, Gm
Rat 606						
0	343					
2				12.7	1.0181	0.014
5		127	17.0			
9	284	43	14.9			
Rat 585						
0	340					
1				8.3	1.0201	0.011
8				8.7	1.0200	
10	286	42				
20				17.3	1.0187	0.086
31		99	12.8			
35	299	82	10.0			
Rat 603						
0	305					
2				17.4	1.0183	0.014
5		127	17.5			
13				10.2	1.0169	
15	273	50				
34				9.6	1.0259	0.009
37		44	11.0			
41	318	73	10.2			

Notes. Rat 606. Two thirds of left kidney removed on May 8, 1931, right kidney removed on May 13. Killed on May 22. Not sick, no pathologic changes. Blood pressure 122, heart ratio 0.180, kidney ratio 0.109.

Rat 585. Two thirds of left kidney removed on May 8, 1931, right kidney removed on May 18. Killed on June 24. Not sick, no pathologic changes. Blood pressure 150, heart ratio 0.215, kidney ratio 0.213.

Rat 603. Two thirds of left kidney removed on May 8, 1931, right kidney removed on May 13. Killed on June 24. Not sick, no pathologic changes. Blood pressure 118, heart ratio 0.216, kidney ratio 0.162.

TABLE 5—*The Early Postoperative Stage in (Apparently) Well, Partially Nephrectomized Animals*

Rat	Weight, Gm	Duration of Experiment, Days	Age at Death, Days	Hemoglobin, Gm per 100 Ce	Heart Weight		Kidney Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Ce	Twenty Four Hour Urine Concentration Test		
					Surface Area × 100	Surface Area × 100				Volume, Ce	Specific Gravity	Albumin, Gm
584	238	1	238		0.202					11.0	1.0168	0.017
599	171	6	275	14.1	0.177					14.0	1.0167	0.006
598	146	6	275	14.3	0.162				119	11.0		
607	228	9	332	12.0	0.209	0.133	102	75		23.2	1.0095	0.005
606	284	9	332	14.9	0.180	0.109	122	43		12.7	1.0181	0.014
605	269	9	332	10.5	0.162	0.068	112	88		16.3	1.0132	0.008
432	98	10	154		0.202	0.084	147	218				
307	205	12	215		0.174	0.215	126			16.5	1.0152	
585	299	37	274	10.0	0.215	0.313	150	52		17.3	1.0187	0.086
587	329	37	274	16.8	0.208	0.218	134	78		11.2	1.0246	0.012
Average					0.189							

from the normal Hypertension as early as the tenth day without cardiac hypertrophy was found in only one case. Similar data as regards nitrogen retention, polyuria, low specific gravity, albuminuria and renal hypertrophy were obtained in a number of animals excluded on account of pulmonary disease.

TABLE 6—*The Late Postoperative Stage in Apparently Well, Partially Nephrectomized Animals*

Rat	Weight, Gm	Duration of Experiment, Days	Age at Death, Days	Hemoglobin, Gm per 100 Cc	Heart Weight	Kidney Weight	Blood Pressure, Mm	Non protein Nitrogen, Mg per 100 Cc	Twenty Four Hour Urine Concentration Test		
					Surface Area × 100	Surface Area × 100			Volume, Cc	Specific Gravity	Albumin, Gm
425	292	43	267	12.2	0.247	0.211	172	106	14.8	1.0121	0.034
128	206	72	295	14.5	0.203	0.178	152	53	4.6	1.0302	0.006
429	344	72	319	13.3	0.218	0.243	120	67	9.4	1.0226	0.077
470	180	72	319	11.1	0.205	0.175	152	39	3.7	1.0274	
774	252	94	220	14.6	0.244	0.335		127	19.2	1.0173	0.128
578	200	98	269	16.1	0.217	0.325	152	83	14.5	1.0182	0.171
475	362	105	333	16.8	0.205	0.360	187		14.3	1.0222	0.272
501	245	112	191	14.9	0.213	0.370	180	91	13.0	1.0247	0.218
501	303	112	185	11.3	0.221	0.445	156	100	20.2	1.0236	0.131
508	173	112	191	12.6	0.227	0.349	162	87	10.3	1.0202	0.197
465	328	112	320	12.7	0.253	0.502	180	133	20.3	1.0175	0.059
505	188	115	192	11.7	0.265	0.412	200	197	12.7	1.0203	0.149
507	160	115	192	11.6	0.228	0.461	196	114	11.3	1.0198	0.173
466	376	116	375	12.0	0.238	0.560	196	111	19.0	1.0190	0.148
493	303	122	257	16.7	0.244	0.533	192	121	16.5	1.0184	0.204
418	167	124	284	13.7	0.222	0.210	166	60	7.4	1.0219	0.096
414	308	124	284	12.8	0.218	0.212	162	38	7.7	1.0312	0.005
166	213	170	238	13.0	0.248	0.493	214	133	13.0	1.0203	0.151
112	202	173	223	12.1	0.179	0.277	126		5.3	1.0387	
115	207	173	223	11.1	0.205	0.176	170	133	11.2	1.0183	0.058
114	216	173	223	14.1	0.176	0.222			8.0	1.0189	0.039
116	209	173	222	15.3	0.164	0.228	116	50	2.0	1.0513	
113	224	173	223	12.5	0.164	0.187	118		3.7	1.0357	
108	234	174	223	13.2	0.204	0.226	150	69	7.7	1.0275	0.132
102	229	174	223	13.9	0.210	0.308	172	103	8.7	1.0250	0.187
106	208	174	223	14.6	0.179	0.208	124	58	3.8	1.0394	
98	296	180	289	15.5	0.211	0.330	152	96	9.8	1.0219	0.063
147	304	182	305	12.8	0.218	0.316	168	93	11.0	1.0204	0.122
91	225	183	344	17.0	0.188	0.222		51	3.2	1.0390	
55	178	187	268	16.0	0.190		128	68	2.0	1.0506	
143	272	197	470	13.7	0.198	0.223	140	79	8.8	1.0263	0.151
66	393	211	316	13.2	0.231	0.603	156	112	16.8	1.0172	0.053
57	168	212	282	11.1	0.256	0.380	190	180	14.1	1.0163	0.213
58	172	212	283	12.0	0.249	0.418	186	121	9.2	1.0171	0.059
3	243	213	495	11.3	0.263	0.417	170	62	10.5	1.0189	0.067
37	296	213	525	15.0	0.267	0.336	220	132	14.1	1.0151	0.036
7	240	216	279	15.6	0.212		169	112	11.3	1.0231	0.136
162	252	216	294	12.8	0.253	0.610	160	74	10.8	1.0268	0.275
7	298	219	307	14.9	0.200	0.193	130	48	9.6	1.0262	0.204
164	261	221	294	13.4	0.190	0.273	110	61	7.9	1.0251	0.114
163	207	225	293	11.8	0.310	0.370	230	174	13.1	1.0206	0.295
Average					0.221		164				

The Late Postoperative Stage in Apparently Well, Partially Nephrectomized Animals—This group includes partially nephrectomized rats that were killed at various intervals beginning forty-three days after the second operation (table 6). In order to eliminate the effects of pulmonary disease and anemia²⁵ on heart size, only those animals with normal lungs and a hemoglobin of more than 11 Gm per

²⁵ Forman, M. B., and Daniels, A. L. Effect of Nutritional Anemia on the Size of the Heart, *Proc Soc Exper Biol & Med* 28:479, 1931.

hundred cubic centimeters of blood are listed in this group. The data presented were obtained shortly before or at the time of death. Observations were made at frequent intervals on each rat so that fairly complete individual histories were available.

The nonprotein nitrogen ranged from 50 to 197 mg per hundred cubic centimeters, agreeing roughly with the degree of renal insufficiency as estimated by the urinary volume and specific gravity. It was of special interest to note the degree of nitrogen retention that could be reached and maintained in an individual rat without appreciable evidences of toxemia.

Despite the fact that the amount of kidney tissue removed was approximately the same in all cases, there was a marked individual difference in the renal function. Furthermore, there seemed to be no relationship between the degree of kidney hypertrophy and kidney function. Histologic study may explain this apparent discrepancy. The specific gravity of the urine varied between 1.0121 and 1.0556. It was not unusual to obtain from 20 to 25 cc of urine during a concentration test. These figures are more striking when it is remembered that the maximum output in the control animals was 5.4 cc. In all these animals, the albuminuria was initially within normal limits, but after periods varying from one to two months a progressive increase was noted. An albuminuria represented by 0.295 Gm of dried protein was the maximum figure obtained. Although casts eventually were found in the urine of all animals having a deficient kidney function, the time of their initial appearance could not be predicted.

The specific gravity of the blood serum was within the normal range. The specific gravity of the whole blood paralleled the hemoglobin values.

The carotid blood pressure readings were striking. They varied from 110 to 230 mm, with most of them well above the upper limits of normal. We found that animals with marked sustained renal insufficiency invariably showed high blood pressure, but that the degree of nitrogen retention could not be used as a criterion for the prediction of hypertension.

In practically all cases of hypertension, the $\frac{\text{heart weight}}{\text{surface area}}$ ratio was increased. In addition definite thickening of the left ventricular wall was noted in many of them. No other gross cardiac abnormality was seen in this group. The percentage of total solids in the hypertensive hearts was no different from that of the controls, thus eliminating the possible effect of water on the increased weight.

The variations in hypertrophy of the kidney were shown by the $\frac{\text{kidney weight}}{\text{surface area}}$ ratios. Immediately after the second operation, the kidney ratio was as low as 0.075, hypertrophy in the kidney remnant progressed rapidly, and in many cases its ratio exceeded the control value of 0.438.

for both kidneys. The total solids in these hypertrophied kidneys varied from 14.2 to 23 per cent, the majority being between 15 and 21 per cent. The hypertrophied kidneys had a fairly typical appearance. The capsule was noticeably thickened and at times adherent. The surface was pale, edematous and yellowish brown. Varying amounts of the ligated stumps remained, depending on the duration of the experiment. Soon after the operation the stumps consisted of an encapsulated mass

TABLE 7—*Protocol of Rat 57*

Time After Operation, Days	Weight, Gm	Nonprotein Nitrogen, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Urine (24 Hour Specimen)		
				Volume, Cc	Specific Gravity	Albumin, Gm
0	103					
53	151	68				
62	156	93				
87				5.5	1.0200	0.000
105				7.5	1.0296	
111	170	78		6.4	1.0276	
136						
175	179		13.9			
173				12.8	1.0158	0.036
201				14.1	1.0163	0.213
212	168	180	11.1			

Notes: Rat 57, Female, aged 70 days. Two thirds of left kidney removed on Sept. 11, 1930; right removed on September 18. Killed on April 17, 1931. Not sick, no pathologic changes. Blood pressure 190, carotid markedly dilated and tortuous, heart ratio 0.256, total solids 22.9 per cent, kidney ratio 0.380, total solids 17.2 per cent, serum specific gravity 1.0260, specific gravity of whole blood 1.0349, urinary sediment contained an occasional granular cast.

TABLE 8—*Protocol of Rat 163*

Time After Operation, Days	Weight, Gm	Nonprotein Nitrogen, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Urine (24 Hour Specimen)		
				Volume, Cc	Specific Gravity	Albumin, Gm
0	92					
37				3.4	1.0416	0.005
86	234	80				
109				5.8	1.0296	
141				14.8	1.0235	0.175
172	224	114				
207				13.1	1.0206	0.295
225	207	174	11.8			

Notes: Rat 163, Female, aged 66 days. Two thirds of left kidney removed on Oct. 23, 1930; right removed on November 3. Killed on June 15, 1931. Not sick, no pathologic changes. Blood pressure 230, carotid markedly dilated and tortuous, heart ratio 0.310, kidney ratio 0.370, urinary sediment contained many hyaline casts.

of necrotic cheeselike material. This was gradually absorbed until a small hard mass remained which in turn finally disappeared entirely. On section the kidney was pale, edematous and yellowish brown with an indistinct cortex.

An occasional animal had a small amount of fluid in the peritoneal or the pleural cavities or in both. "Wet" subcutaneous tissue was encountered in a few rats. Since these findings were so unusual in our experimental animals, they were not considered a part of the typical syndrome encountered in experimental kidney insufficiency.

Tables 7, 8 and 9 illustrate the most typical changes in individual animals in this group. The urinary changes recorded in table 7 are most representative of the majority of partially nephrectomized animals. There was a gradual decrease in the specific gravity and an increase in the urinary volume. The albuminuria became pronounced after the second month. The nonprotein nitrogen was elevated but not exceedingly high. Table 8 shows an animal which soon after operation had an apparently normal kidney function, but after a few months the

TABLE 9—*Protocol of Rat 425*

Time After Operation, Days	Weight, Gm	Nonprotein Nitrogen, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Urine (24 Hour Specimen)		
				Volume, Cc	Specific Gravity	Albumin, Gm
0	285					
9				13.6	1.0166	0.012
36				14.8	1.0121	0.034
40	292	106	12.2			

Notes: Rat 425, Male, aged 214 days. Two thirds of left kidney removed on Feb. 2, 1931, right removed February 11. Killed March 23. Animal slightly weak, no pathologic changes. Heart ratio 0.247, kidney ratio 0.211, blood pressure 172, carotid markedly dilated and slightly tortuous, kidney stumps markedly atrophied.

TABLE 10—*Partially Nephrectomized Animals Killed While in Good Health Showing Moderate Anemia*

Rat	Weight, Gm	Duration of Experiment, Days	Age at Death, Days	Hemoglobin, Gm per 100 Cc	Heart Weight	Kidney Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty Four Hour Urine Concentration Test		
					Surface Area × 100	Surface Area × 100			Volume, Cc	Specific Gravity	Albumin, Gm
593	149	40	120	8.0	0.197	0.143	142	179	12.6	1.0146	0.013
596	168	42	310	9.9	0.190	0.287	144	89	11.6	1.0187	0.009
601	233	42	207	7.6	0.222	0.187	126	94	11.7	1.0193	0.053
368	213	69	193	9.3	0.290	0.270	166	189	16.2	1.0129	0.016
559	111	72	270	7.0	0.245	0.236	194	206	11.4	1.0149	0.022
552	278	96	244	9.7	0.253	0.422	170	133	17.5	1.0166	0.112
531	250	100	250	8.3	0.216	0.330	134	87	15.8	1.0195	0.147
553	185	101	283	8.9	0.187	0.213	124	104	10.5	1.0173	0.056
480	278	109	268	8.9	0.219	0.362	156	98	15.3	1.0209	0.121
479	262	109	269	9.7	0.261	0.383	178	154	22.0	1.0205	0.455
364	214	115	239	6.6	0.260	0.281	214	218	14.6	1.0165	0.073
532	256	123	231	6.5	0.254	0.430	186	220	20.8	1.0125	0.043
439	338	133	272	9.5	0.296	0.255	184	77	15.3	1.0196	0.250
Average					0.233		163				

characteristic "nephritic" changes in specific gravity, urinary volume and albuminuria developed. The animal in table 9 was chosen to illustrate a continued high urinary volume and a low specific gravity from the time of the second operation. In this case there was hypertension without marked albuminuria.

The Late Postoperative Stage in Partially Nephrectomized Animals with Anemia—Partially nephrectomized animals killed while in good health but showing a moderate anemia are grouped in table 10. The outstanding difference between this and the preceding group is the large

volume of urine with uniformly low specific gravity. Despite the anemia there seemed to be a fairly good correlation between the blood pressure and the heart ratio. It should be pointed out that the degree of anemia was not so great as noted in cases of nutritional anemia²⁵. An occasional rat showed poor renal function without hypertension or cardiac hypertrophy. The tremendous albuminuria noted in some of the partially nephrectomized animals is worthy of mention. Rat 479 excreted 0.455 Gm of protein in twenty-four hours, which represents about one-half its total circulating plasma protein. The absence

TABLE 11—*Partially Nephrectomized Animals Living Less Than Forty Days and Killed While Acutely Ill*

Rat	Weight, Gm	Duration of Experiment, Days	Age at Death, Days	Heart Weight	Kidney Weight	Blood Pressure, Mm	Non protein Nitrogen, Mg per 100 Cc	24 Hour Urine Concentration Test		Degree of Illness
				Surface Area × 100	Surface Area × 100			Volume, Cc	Specific Gravity	
390	173	3	170	0.168	0.058	104	250			4+
389	227	3	165	0.200	0.097	108	308			4+
387	240	3	169	0.194	0.064	120	320			4+
380	238	3	241	0.172	0.098	96	111			4+
381	239	3	219	0.193	0.067	138	267			4+
399	147	3	122	0.196	0.087	116	364			4+
303	135	5	151	0.208	0.091	110	445			4+
301	164	5	151	0.194	0.123	100	325			4+
401	255	7	141	0.210	0.121	90	226			3+
400	176	7	141	0.214	0.092	94	454			4+
195	165	7	279	0.220	0.093	94	348			4+
427	151	8	234	0.166	0.063	96	276			3+
358	273	10	345	0.223	0.114	110	348			3+
308	183	12	215	0.172	0.149	80	250	17.0	1.0135	4+
309	207	12	215	0.168	0.121	110	210	14.8	1.0150	3+
311	113	18	163	0.203	0.114	92	416			4+
459	186	19	270	0.187	0.125	90	370	14.7	1.0128	3+
317	166	32	220	0.182	0.151	110		16.0	1.0144	2+
Average				0.198	0.101	103	310			

of any correlation between blood pressure and nitrogen retention is again emphasized in this group.

Partially Nephrectomized Animals Killed While Ill—Animals included in this group were killed because of their poor condition and imminent death. The signs 1 to 4+ were used as a rough method of indicating the degree of illness of a rat. A 4+ animal was practically moribund at the time it was killed. The 3+ and 2+ animals probably could not have survived more than from twenty-four to forty-eight hours. The 1+ animals were in fairly good condition, but showed ruffled hair and an acute loss of weight.

Partially Nephrectomized Animals Acutely Ill—All rats living less than forty days have been included in this group (table 11). The heart ratios were practically normal despite the fact that most of these animals lost between 40 and 50 per cent of their body weight. The results were

only approximate since the surface area formula used was not intended for animals showing acute loss in body weight. The kidney ratios were relatively low when compared to those of well animals killed during this same period. Obviously too much kidney tissue had been removed. The blood pressures were markedly lowered, but were comparatively high considering the moribund condition of the rats. This seemed to be characteristic of all the animals suffering from acute cachexia. The nonprotein nitrogen in this group represented the highest degree of

TABLE 12—*Partially Nephrectomized Animals Becoming Ill After Forty Days*

Rat	Weight, Gm	Duration of Experiment, Days	Age at Death, Days	Hemo globin, Gm per 100 Cc	Heart Weight	Kidney Weight	Blood Pressure, Mm	Non protein Nitro gen, Mg per 100 Cc	24 Hour Urine Concentration Test			Degree of Illness
					Surface Area × 100	Surface Area × 100			Vol ume, Cc	Specific Grav-ity	Albu min, Gm	
549	159	49	195		0.230	0.204	30		17.4	1.0160	0.035	4+
422	193	56	221	11.6	0.279	0.217	118	129	10.2	1.0150	0.010	2+
363	224	59	183	10.5	0.242	0.286	102	89	6.5	1.0244	0.119	4+
572	202	60	367	16.5	0.232	0.303	175	200	16.2	1.0136	0.028	4+
471	202	62	245	13.3	0.252	0.228	180	131	19.3	1.0148	0.027	2+
546	217	67	224	8.9	0.262	0.349		171	18.3	1.0162	0.128	3+
556	177	68	250	15.3	0.229	0.218	104	59	9.8	1.0243		3+
569	282	69	379	17.0	0.226	0.340	90	123	10.4	1.0245	0.053	4+
323	238	70	277	14.8	0.286	0.210	126	129	14.4	1.0167	0.167	4+
370	203	72	195	6.6	0.270	0.143	154		17.8	1.0120	0.005	3+
530	159	72	220	11.2	0.246	0.282	166	125	9.6	1.0214		3+
436	272	74	125	15.6	0.252	0.389		72	6.5	1.0312	0.003	4+
558	149	83	262	14.9	0.220	0.200	100		11.5	1.0159	0.128	4+
576	174	90	260	12.2	0.234	0.252	172	163	13.2	1.0194	0.156	3+
478	228	91	246	9.4	0.287	0.287	156	220	25.7	1.0143	0.082	2+
481	203	93	248	13.8	0.289	0.251	165	221	20.0	1.0147	0.084	3+
467	264	96	302	13.9	0.263	0.453	204	168	20.4	1.0168	0.153	4+
535	161	97	229	10.3	0.245	0.282	170	200	11.3	1.0167	0.135	2+
50	163	105	391		0.324	0.316	160	260	10.8	1.0135		4+
57	150	118	199		0.252	0.262	152	135	9.9	1.0169		4+
59	144	121	201		0.238	0.293	174	122	7.0	1.0226		4+
42	217	140	336		0.298	0.359	140	88	8.5	1.0235		4+
4	180	141	419		0.266	0.300	70	204	11.0	1.0143		2+
137	179	162	200	12.0	0.231	0.176			15.8	1.0159	0.054	3+
56	187	197	270	11.5	0.226	0.500		76	6.6	1.0291	0.170	4+
97	153	200	415	12.9	0.308	0.410	190	96	12.7	1.0176	0.117	4+
40	236	211	395	9.0	0.302	0.450	178		12.4	1.0182	0.170	2+
39	251	212	393	17.0	0.276	0.292	55	222	18.5	1.0180	0.275	3+
Average					0.259	0.294		148		1.0180		

nitrogen retention encountered in our experiments. When concentration tests were done, marked polyuria and low specific gravity resulted.

Partially Nephrectomized Animals Becoming Ill After Forty Days—Data for these animals are listed in table 12. After maintaining or increasing their weights for various lengths of time, they generally showed a marked and rapid loss of weight. During the terminal stage these rats became sluggish, with ruffling of their hair and rapid respiration. Muscular tremors were usually present, and occasional convulsions were seen. Partial paralysis of the hind legs was observed in a few animals. The same syndrome was noted in many of the "acutely ill" animals already discussed.

The nonprotein nitrogen was uniformly elevated but showed wide variations. The urinary volumes and specific gravities indicated a

consistently low renal function. The blood pressures were extremely variable. The heart ratio was uniformly well above normal, and the carotid arteries were invariably dilated, these two findings, in our experience with less affected rats, were characteristic of hypertension. Therefore, we think that all of the animals in this group would have shown hypertension at some time had repeated blood pressure observations been possible during the postoperative period. We believe that the low blood pressures were explicable on the basis of the imminency of death. It must be pointed out that many of these rats lost a great deal of weight during the terminal period, thus causing our surface area measurements to be merely approximate. However, a comparison with the heart ratios in table 11 leaves no doubt concerning the question of cardiac hypertrophy.

COMMENT AND CONCLUSIONS

The variations in the minimum quantities of kidney tissue needed by various species are of interest. It appears from work done by previous investigators that dogs die if more than three fourths of the kidney tissue is removed.²⁶ The goat apparently lives in good health with but one fifth of one kidney.¹¹ The rabbit seems incapable of surviving if more than from 60 to 70 per cent of the renal tissue is excised.¹⁰ The removal of three fourths of the kidney substance in the cat is followed by death within a relatively short time.⁴ Rats with one half of one kidney have a normal kidney function, but a sixth of the total kidney tissue, in our experience, is the minimum compatible with life.

Our results are in accord with those of Passler and Heinecke,³ who observed that ischemic kidney tissue disappeared and that it had no relation to elevation of the blood pressure. Although Cash⁹ concluded that the preliminary rise of blood pressure in the dog shortly after partial nephrectomy was dependent on the presence of necrotic tissue, in our work the hypertension appearing after an appreciable interval was not affected by the removal or retention of the ligated tissue.

Impaired renal function, characterized by polyuria and nitrogen retention, was encountered in the majority of partially nephrectomized rats shortly after the second operation. The degree of polyuria in animals showing no indication of increased blood pressure was often as great as that encountered in hypertensive rats. Hence it was thought that the increased flow of urine of low specific gravity was not solely dependent on the presence of hypertension. The polyuria, so striking in a number of animals immediately after the second operation, was, in the absence of hypertension, probably due to an increased permeability

26 Bradford (footnote 2) Pässler and Heinecke (footnote 3) Allen, Scharf and Lundin (footnote 11)

of the glomerulus. When pathologic changes in the renal tissue (as judged by the increases in albuminuria, polyuria and nonprotein nitrogen in the apparently well animal) became obvious, an increase in the blood pressure was generally noted (table 6). The assumption seems warranted that in partially nephrectomized rats with renal insufficiency, an increase in blood pressure is necessary to maintain an increased volume of urine in order to excrete metabolites in lower concentration. Apparently this compensating mechanism fails when there is excessive damage to the remaining renal parenchyma (table 12), just as it fails when too much renal tissue is removed (table 4). Our evidence indicates that the polyuria in the partially nephrectomized rat, reaching the stage of chronic renal insufficiency, depends to a great extent on an increased blood pressure.

On the basis of perfusion experiments and theoretical consideration, Verney²⁷ postulated as follows: "In the whole animal, therefore, it would not be surprising to find that when this second reserve of the kidney was exhausted and all the renal units were receiving the maximum stimulus which under the circumstances could be given them, and yet were unable to cope with the work thrust upon them there should be a call for external aid in the form of a rise in the general blood pressure." This idea is certainly supported by our experimental data.

Nitrogen retention, although to a varying degree, characterized the results obtained in partially nephrectomized rats in this series. The highest nonprotein nitrogen invariably occurred in animals becoming ill shortly after the second operation, a value of 454 mg. was obtained in one case. The average results were higher than those seen in the completely nephrectomized rat²⁸. This difference can probably be explained on the basis of a greater duration of time for the accumulation of metabolites in the partially nephrectomized rat. A marked increase in nitrogen retention was invariably indicative of the terminal stage. However, the severity of the illness was not in all cases comparable to the degree of nitrogen retention, since many moribund animals showed comparatively low concentrations of nonprotein nitrogen. Furthermore, a chronic moderate elevation of the nonprotein nitrogen had no demonstrable effect on the general health of the animal.

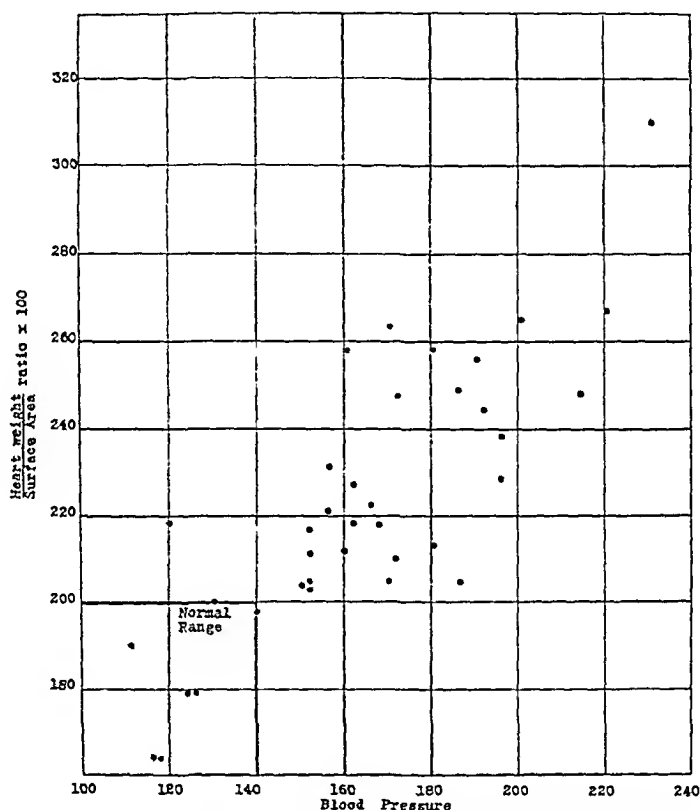
Passler and Heinecke³ stressed their failure to obtain hypertension in dogs becoming cachectic shortly after or during the course of their repeated operations. The necessity of good health was emphasized as a factor in the development of a high blood pressure. Our findings

27 Verney, E. B. Polyuria in Chronic Nephritis, *Lancet* **1** 751, 1929.

28 Chanutin, A., and Silvette, H. A Study of Creatine Metabolism in the Nephrectomized White Rat, *J. Biol. Chem.* **85** 179, 1929.

verify these conclusions. In our experiments, those animals losing weight and developing marked evidences of "uremia" showed definitely lower blood pressures than the controls (table 11)

It has been pointed out that but two groups of investigators³⁰ have been able to produce hypertension associated with cardiac hypertrophy as a result of partial nephrectomy. The data in table 6 have been used to show the relationship between hypertension and the $\frac{\text{heart weight}}{\text{surface area}}$ ratio (see the accompanying chart). A statistical analysis of these data by



Relationship between hypertension and the $\frac{\text{heart weight}}{\text{surface area}}$ ratio

the use of the Pearson product-moment formula yielded a correlation coefficient (r) of 0.86 ± 0.028 . This means that there is a high positive relationship between the $\frac{\text{heart weight}}{\text{surface area}}$ ratio and blood pressure. Such a finding must lead to the conclusion that in these experiments cardiac hypertrophy is a constant and proportional accompaniment of hypertension. As far as we know, this is the first experimental demonstration of such a relationship. We believe that the hypertension and cardiac hypertrophy obtained in these experiments are definitely dependent on the renal insufficiency produced by partial nephrectomy.

30 Pässler and Heinecke (footnote 3) Mark and Geisendorfer (footnote 12a)

SUMMARY

By reducing kidney tissue to a minimum compatible with life, chronic renal insufficiency has been reproduced with constancy in a sufficient number of rats. The striking features of this study were the progressive development of polyuria, albuminuria, nitrogen retention, renal hypertrophy, hypertension and cardiac hypertrophy. Edema did not appear, the specific gravity of the serum was constant, and there was a tendency toward a moderate anemia.

ACUTE BACTERIAL ENDOCARDITIS DUE TO BACTERIUM ACIDI-LACTICI

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While bacterial endocarditis is common, endocarditis due to *Bacterium acidi-lactici* appears to be unique, at least. I have found no other case in the literature Winslow¹ considered this micro-organism to be a separate species in the *Bact coli* group, although Topley and Wilson² regarded it as one of the varieties of *Bact coli* Ford³ placed it in the *Bact mucosum-capsulatum* group, and suggested for it the name *Bact duodenale*

It was first described by Hueppe⁴ in 1884 It resembles the other bacilli of the colon group It is gram-negative, nonmotile and non-sporulating It forms indole reduces nitrates, coagulates milk and does not liquefy gelatin It is found in milk, water and the intestinal tract of man It is distinguished from other types of *Bact coli*, from *Bact lactis-aerogenes*, and from Friedlander's bacillus by its characteristic sugar fermentations It ferments dextrose, lactose, adonite and mannite, but does not ferment saccharose, dulcitol, salicin, inositol, raffinose, xylose or inulin It does not produce so much gas as *Bacillus lactis-aerogenes*⁵ At the Presbyterian Hospital it is routinely differentiated from the other organisms in the group by its lack of power to ferment saccharose and salicin

The only example of infection with *Bact acidi-lactici* found in the available literature was reported by Ray⁵ in 1923 a case of meningitis in which the micro-organism was isolated from the blood and spinal fluid It is possible that *Bact acidi-lactici* infections in man may have been reported among the cases of *Bact coli* sepsis Ray attributed this

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1 Winslow, E, Kligler, E, and Rothberg, A Studies on Colon-Typhoid Group of Bacteria, *J Bact* 4 429, 1919

2 Topley, W W C, and Wilson, G S Principles of Bacteriology and Immunity, New York, William Wood & Company, 1929, vol 1, p 425

3 Ford, W W Text Book of Bacteriology, Philadelphia, W B Saunders Company, 1927, p 556

4 Hueppe, F Untersuchungen uber die Versetzungen der Milch durch Micro organismen, *Arb a d k Gsndhtsamte* 2 309, 1884

5 Ray, H M Fatal Case of *Bacillus Acidi Lactici* Meningitis, *J Lab & Clin Med* 8 260, 1923

to the use of impure carbohydrate in making the fermentation tests and to the fact that the micro-organisms occasionally lose their original fermentative powers when cultured

Several cases of endocarditis due to *Bact coli* have been reported (Lenhartz,⁶ Horder,⁷ Norris,⁸ Jochmann,⁹ Summe,¹⁰ Jacob¹¹)

It is a strange coincidence that two cases of endocarditis due to *Bact acidilactici* should have occurred in the Presbyterian Hospital within a short time of each other

CASE 1—The patient, R B, was admitted on Nov 8, 1930, to the genito-urinary service of Dr Squier, Dr George Cahill attending¹² His complaints were frequency of micturition and nocturia His family history was not important The only previous illness of interest was a mastoiditis with operation two and one-half years before The mastoid had to be reopened in two weeks, but it healed well with no evidence of residual infection His present illness began abruptly, two days before admission, with marked frequency of urination, nocturia and fever The temperature was 102 F, the pulse rate 96, respirations 20 and blood pressure 144 systolic and 60 diastolic The patient was an elderly, obese man, acutely ill The chest and abdomen were normal on examination The heart sounds were of fair quality, and no murmurs were heard The prostate was prominent, soft and tender There was slight hematuria after the rectal examination

The following laboratory observations were made

Blood Count

	Red Blood Cells	White Blood Cells	Polymorpho- nuclears, per Cent
Nov 12	3,700,000	10,000	86
Nov 19	3,400,000	27,850	92
Dec 1	3,450,000	15,000	91
Dec 10	3,000,000	26,400	89

Urinalysis showed cloudy, acid urine, specific gravity, 1.016, albumin, ++, diacetic acid, ++++, many red blood corpuscles and white blood corpuscles The blood urea content was 44.1 mg per hundred cubic centimeters, the carbon dioxide content, 71 per cent by volume

6 Lenhartz, H Die septischen Erkrankungen, Vienna, A Holder, 1903

7 Horder, T J Infective Endocarditis with an Analysis of 150 Cases with Special Reference to the Chronic Form of the Disease, Quart J Med 2 289, 1909

8 Norris, G W Studies in Cardiac Pathology, Philadelphia, W B Saunders Company, 1911, p 26

9 Jochmann, G Ueber Endocarditis septica, Berl klin Wchnschr 49 436 1912

10 Summe, quoted by Kraus, F, and Brugsch, T Spezielle Pathologie und Therapie innerer Krankheiten, Berlin, Urban & Schwarzenberg, 1913, vol 2, pt 2, p 1164

11 Jacob, L Ueber Allgemeininfektion durch Bacterium coli commune, Deutsches Arch f klin Med 97 303, 1909

12 This case was the subject of a paper read before the New York Pathological Society in April, 1931

The patient's temperature rose to 106 F on November 10. On November 15, an external urethrotomy with incision and drainage of the prostatic abscess was performed. Several drachms of pus were removed. No culture was taken. The patient was irrational but had no signs of increased intracranial pressure or meningeal irritation. A blood culture on November 17 was positive, a gram-negative bacillus was isolated which was later identified as *Bact acidilactici*. A blood culture on November 26 was sterile. On November 29 the temperature indicated sepsis. A blood culture on December 2 was positive, the micro-organism was reported to be a bacillus in the Friedlander group, but not a true *B mucosus-capsulatus*. On December 3 a physical examination revealed dulness at the base of the right lung, with râles in the base of the left lung. On December 4, broncho-vesicular breathing was present in the left side in addition to the râles. A loud systolic and a soft diastolic murmur was heard for the first time. The lung signs continued changing from day to day. On December 7, petechiae were found in the left conjunctiva, and the fingers on the right hand were painful. The murmurs were more pronounced. At this time the diagnosis of bacterial endocarditis was made, although the micro-organism obtained in blood cultures was not as yet accurately identified. Petechiae appeared elsewhere, in addition, the right wrist became painful and swollen. On December 10 the patient was slightly irrational. On December 11 he was exceedingly irrational and developed meningismus in the afternoon. That evening he suddenly became livid, and his pulse rate dropped to 48. He died thirty-five days after admission and twenty-seven days after the operation. The clinical diagnoses were subacute bacterial endocarditis, due to *Bact acidilactici*, and abscess of the prostate.

Autopsy—Autopsy was performed nine and a half hours post mortem. There were many petechiae in both conjunctivae and in the skin of the trunk and upper extremities. The perineal incision was clean and not draining. The most striking observations were on the heart, although most of the other organs showed changes.

The heart weighed 500 Gm. The auricles were covered with thick, gray, firmly adherent membrane. The right auricle was normal. The tricuspid valve was thin and delicate. At the base of the septal leaflet was a nodule about 0.5 cm in diameter. On section an abscess was found in the wall of the auricle, surrounded by a hemorrhagic area. This extended to the base of the valve. The right ventricle was dilated and hypertrophied. The pulmonic valve was normal. In the left auricle there was an elevated hemorrhagic area in the fossa ovalis. The mitral valve was slightly thickened at the line of closure. Several small hemorrhagic areas were present in the base of the valve. A hemorrhagic area, about 3 mm in diameter, was present in the posterior papillary muscle. The left ventricle was hypertrophied and dilated. The aortic valve leaflets were covered with vegetations which were soft, crumbly and pale yellow. The largest vegetation was 2.5 cm in length and 1.5 cm in thickness, and entirely covered the right posterior leaflet. This leaflet was ulcerated, leaving an opening about 2 mm in diameter. Extending from this were small masses growing down over the endocardium of the left ventricle and the aortic leaflet of the mitral valve, and to the base of the tricuspid valve through the muscle. The areas to which the vegetations were adherent were hemorrhagic. The myocardium was firm, with no visible fibrosis. The coronary arteries were mildly sclerotic.

The aorta was moderately sclerotic.

The lungs were voluminous and covered with smooth pleura. Each weighed 840 Gm. They were crepitant throughout.

The spleen was enlarged and soft On section the pulp bulged over the capsule The liver was normal

The gallbladder was large and filled with thick greenish-black bile Two stones, each about 1.5 cm in diameter, were present The gall bladder wall was thickened The pancreas and suprarenals were normal

The kidneys each weighed 260 Gm The capsule of the right kidney stripped easily, leaving a very finely granular surface, which was pale yellowish-green with many small light yellow areas On section the color was yellowish brown The cortex was 8 mm in thickness Small abscess cavities filled with yellowish pus were present Many tubules were seen in the pyramids as yellowish stripes The left kidney had a more granular surface The color was yellowish-brown with

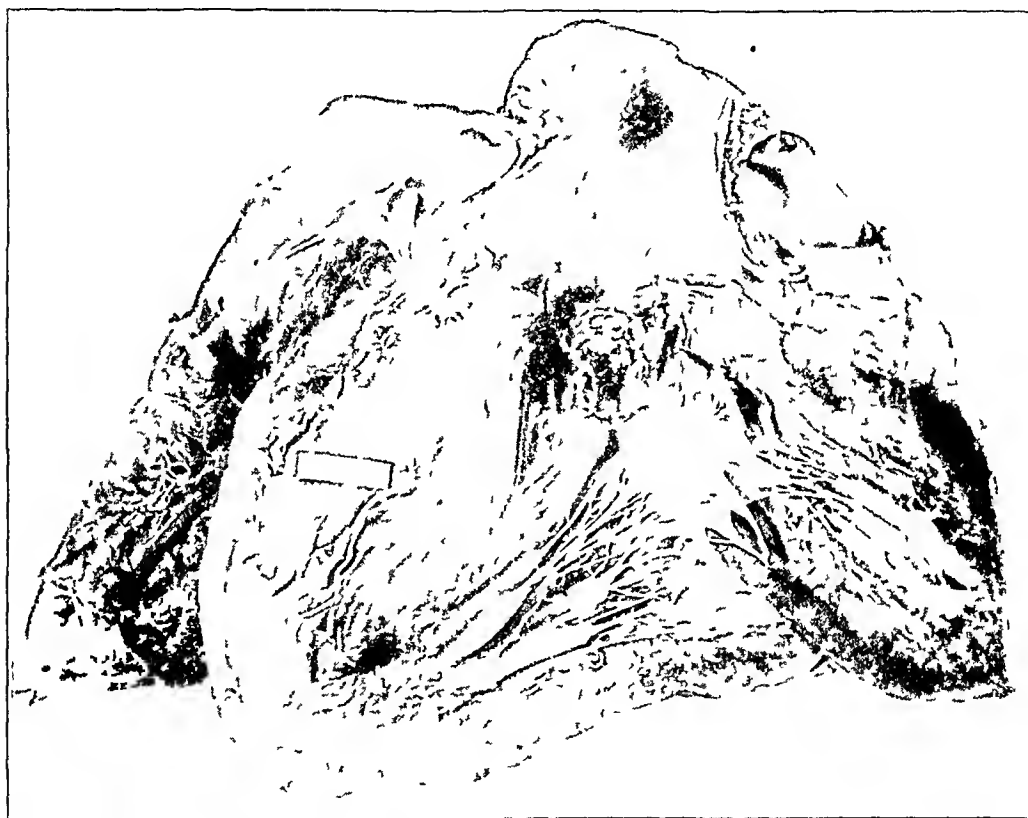


Fig 1—Acute bacterial endocarditis of the aortic valve (*Bact acid-lactici*)

small elevated yellowish areas On section the color was pale reddish brown The cortex was thin, measuring 5 mm in thickness Red longitudinal stripes were present The pyramids were made up of alternate stripes of red and yellow In them were several large abscess cavities up to 1.5 cm in diameter, filled with pus The bladder was thick-walled The prostate was firm and asymmetric, and not enlarged The left side was larger The capsule was indistinct and merged with the periprostatic tissue Many small pus-filled abscesses were present The seminal vesicles and testes showed no changes The gastro-intestinal tract was normal

The brain weighed 1,450 Gm Externally there was a hemorrhagic area on the parietal lobe of the right cerebral hemisphere close to the midline On section many small pale red areas were found scattered through the cerebral hemispheres, internal capsules, cerebellar hemispheres and medulla The spinal cord was not removed

Bact acid-lactici was obtained in pure culture from the heart's blood

Microscopic Examination Sections of the heart, kidney and prostate showed the most marked changes

In the myocardium were areas of polymorphonuclear infiltration and atrophy. Bacterial plugs filled many of the blood vessels. These were made up of short, plump rods which stained deep blue in the hematoxylin and eosin and methylthionine chloride, U S P (methylene blue), sections and red in the Gram stains. In a section of the posterior papillary muscle atrophied muscle fibers were found in the polymorphonuclear-infiltrated reticulum. Hyaline material replaced part of the myocardium. Necrotic muscle fibers were present in these masses. A section of the myocardium taken from a point near the aortic valve showed thickening of the endocardium and subendocardial layers. Part of these structures were infiltrated

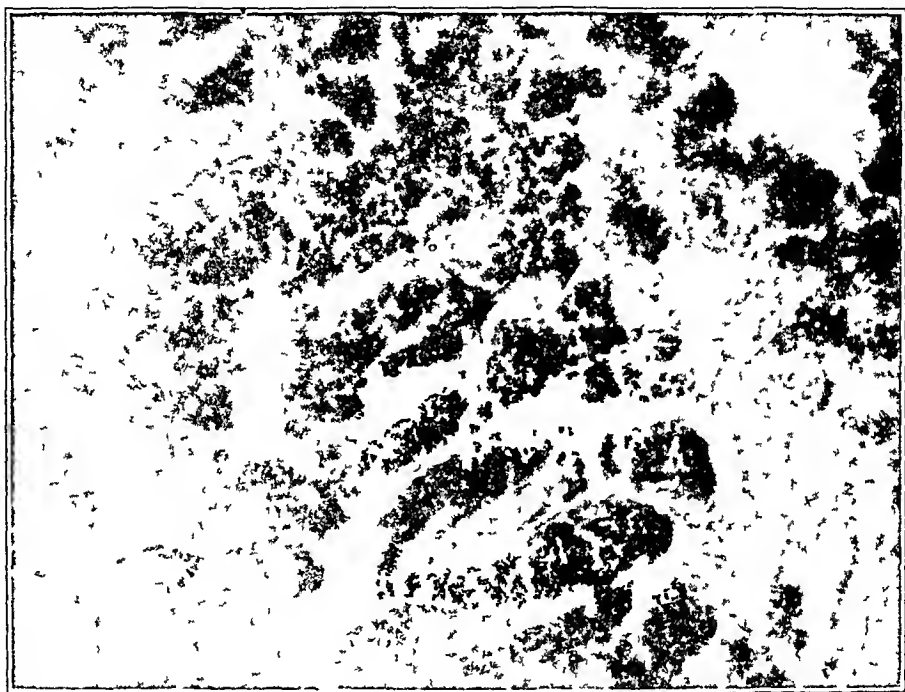


Fig 2—Photomicrograph, taken with the oil-immersion lens, of the vegetation on the aortic valve. Bacterial colonies, composed of large gram-negative bacilli, are seen.

with red blood cells and polymorphonuclear leukocytes, and then were replaced by a mass of fibrin containing many polymorphonuclear leukocytes, bacilli and necrotic debris. The necrosis extended into the myocardium, with the formation of an abscess. The muscle fibers around this area were necrotic and disintegrated. A methylthionine chloride section showed the presence of many bacilli.

The entire aortic valve leaflet taken for microscopic study was necrotic. The surface was covered with vegetations containing large masses of bacteria, polymorphonuclear leukocytes and nuclear debris. The micro-organism was found to be a gram-negative bacillus.

The aorta showed the changes of moderate arteriosclerosis.

The lung sections were normal.

In the liver sections, many polymorphonuclear leukocytes were found which were most numerous in the periportal fields. In many areas masses of bacteria were also present.

The gallbladder was thick-walled. The submucous layer was congested and infiltrated with plasma cells.

In the pancreas the polymorphonuclear leukocytes were increased in number in a few areas where the acini were shrunk or disintegrated.

The amount of lipid material in the cortex of the suprarenals was diminished. Blue-staining bacterial plugs were found in several blood vessels.

Several sections of the kidney examined contained abscess cavities of varying sizes in the cortex and medulla. Areas of round cell infiltration were present. Bacterial plugs were found in several glomerular tufts. Bacilli could be seen throughout the section in the methylthionine chloride preparation.

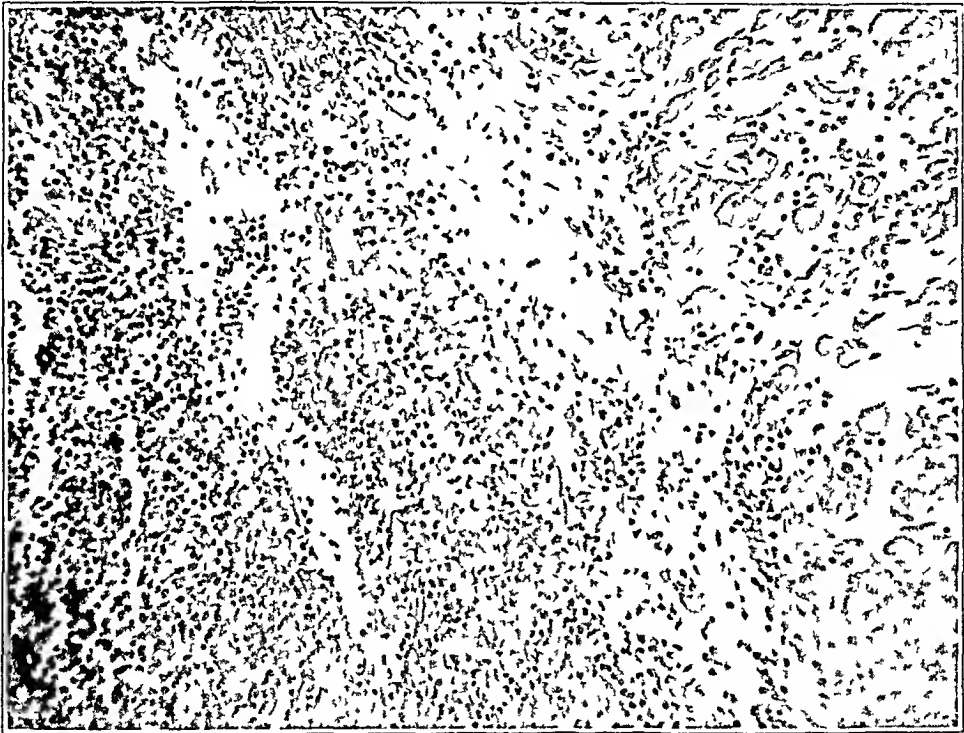


Fig 3—Photomicrograph, taken with the low power objective, of abscess in the myocardium of the interventricular septum. There is a dense infiltration of polymorphonuclear leukocytes and destruction of the muscle fibers.

The prostate showed variations in the size of the acini, which contained desquamated cells and debris. In a few, necrotic material and polymorphonuclear leukocytes were found. The stroma was infiltrated with round cells. A portion of the bladder which was present was infiltrated with round cells. In another section the prostatic tissue had undergone necrosis. Many polymorphonuclear leukocytes and necrotic debris were found in these areas. Dense round and plasma cell infiltrations were present in the stroma. Many bacilli were seen in the abscesses in the methylthionine chloride sections.

The tubules of the testes had thickened basement membranes. Several blood vessels were present whose walls and surrounding tissue were infiltrated with polymorphonuclear leukocytes and round and plasma cells.

The pituitary gland was normal. Several sections of the cerebrum were examined. In one localized area the meninges were infiltrated with many poly-

morphonuclear leukocytes and round cells Bacterial plugs occluded several blood vessels in the substance of the cerebrum About these vessels were found polymorphonuclear leukocytes and round cells, which for the most part were sharply perivascular, in only one area was the brain itself involved In the basal ganglions and cerebellum were found areas of slight perivascular infiltration of round cells

The anatomic diagnosis was chronic and acute prostatitis, abscess of the prostate (external urethrotomy, perineal incision and drainage of prostatic abscess), cystitis cystica, acute bacterial endocarditis (*Bact acidilactici*) of the aortic valve, with extension to the mitral and tricuspid valves, bacteremia (*Bact acidilactici*) with metastases in the myocardium, pancreas, liver, kidneys, testes, brain and leptomeninges, acute splenic tumor, chronic cholecystitis, and cholelithiasis, with calculi in the gallbladder

CASE 2—The patient, E F, was admitted on May 10, 1931, to the genito-urinary service, Dr J B Squier attending Her complaints were chills, fever and nausea About eighteen months before admission she had an attack which resembled the present one Seven weeks before admission she had mild urinary symptoms accompanied by a low grade pyrexia She apparently recovered completely in four weeks For a period of two weeks she was well and able to get about About six days before admission there occurred a relapse She began to have daily chills and a rise of temperature to 105 F She had nausea and some loss of weight, but no other gastro-intestinal or gallbladder symptoms There was no pain during this time Her urinary symptoms were very mild There was no frequency, dysuria or hematuria Because of the nausea her water intake was small She was incontinent and irrational the day before admission The temperature was 101.5 F, the pulse rate 128, respirations 28 and the blood pressure 154 systolic and 76 diastolic She was a woman 63 years old who appeared acutely ill and restless but rational Bronchial râles and slight changes in the breath sounds were noted in the lung examination Examination of the heart revealed that it was overactive and enlarged, the sounds were clear A loud systolic murmur was heard at the apex, which was transmitted to the precordium and axilla Both kidneys were palpable, the right was larger and movable

The following laboratory observations were made The blood count showed red cells 4,050,000, hemoglobin 90 per cent, white cells 36,000 and polymorphonuclear leukocytes 92 per cent Urinalysis revealed albumin + and sugar + (once in four examinations), many white blood corpuscles and a few red blood corpuscles A blood culture showed *Bact acidilactici* A roentgenogram revealed an enlarged heart

The patient had daily chills followed by a marked rise in temperature On May 10, the peak was 103 F On May 11 there were two episodes The peaks were 104 and 106 F On May 12, the temperature reached 104.5 F A physical examination revealed that the heart was slightly larger than on admission, with a marked heaving apical impulse A systolic murmur replaced the final sound The blood culture showed several hundred colonies of *Bact acidilactici* on the plate Petechiae were observed for the first time On May 13, the temperature reached 105 F after a severe chill This was followed by profuse diaphoresis and coma Several new petechiae appeared Signs of bronchopneumonia were noted in the right upper and left lower lobes The pulse rate and temperature continued increasing, the latter reaching 107 F at the time of exitus

Autopsy—The body was that of a rather obese white woman A fading petechia was seen in the left conjunctival sac The heart weighed 350 Gm A large milky plaque was present over the anterior surface at the base of the right ventricle The

right auricle was slightly dilated. The tricuspid leaflets were slightly thickened near the free margin. The right ventricle was normal, as were the pulmonic leaflets. The left auricle was slightly dilated. The mitral leaflets presented several areas of thickening near the free margin, but were competent. The papillary muscles were pale. The left ventricle was slightly dilated. On the right anterior leaflet of the aortic valve was an irregular grayish-red vegetation measuring about 1 cm in its longest diameter. It felt fairly firm and projected toward the ventricular cavity. The other two leaflets of the aortic valve were normal. The myocardium felt fairly soft. The coronary vessels showed numerous grayish-yellow subintimal thickenings. The aorta showed changes of moderate arteriosclerosis. In the lungs, a few firm areas were felt in the lower lobes, otherwise they were normal. The spleen was soft, and on section the pulp overflowed the cut surface. The malpighian corpuscles were not distinct. The liver had a distinct yellowish tinge. The lobulations were distinct in some areas and obscure in others. The gallbladder was considerably distended, and was filled with about 35 cc of pale greenish-brown turbid fluid which was not viscous. Within the gallbladder were four small faceted stones measuring about 1 cm in their longest diameter. A similar stone was found in the cystic duct. The hepatic and common bile ducts were patent. The mucosa of the gallbladder over large areas was gangrenous and necrotic, and in parts separated from the underlying muscular wall. To the external surface of the fundus of the gallbladder the second portion of the duodenum was firmly adherent. The pancreas was normal. The surface of the kidneys was fairly smooth. Several depressed, irregular scars were present. The surface was yellowish gray. On the left kidney was an irregular reddish area about 1 cm in diameter. On section, this extended into the cortex for about 8 mm and was surrounded by a red zone, 2 mm thick. Otherwise the cortex and medulla of both kidneys were normal. The pelvis and ureters were slightly injected. The bladder and genital organs were normal. There were numerous small punctate hemorrhages beneath the mucosa of the stomach. The duodenum was firmly adherent to the gallbladder. The remainder of the intestinal tract was normal. The brain and spinal cord were not removed. **Bacteriologic Report.** *Bact acidilactici* was isolated from the heart's blood and *Bact acidilactici* and *Bact coli* were isolated from the gallbladder.

Microscopic Examination. The myocardium showed no changes. On the aortic valve was a large, irregular vegetation, consisting mostly of pinkish-staining, irregular strands of fibrin. On the surface were large masses of blue-staining bacteria. Near the surface between the fibrinous strands were dense accumulations of poorly preserved erythrocytes and masses of polymorphonuclear leukocytes. The ground substance of the valve was slightly edematous and densely infiltrated with polymorphonuclear leukocytes. Near the tip of the valve was a small isolated vegetation consisting of closely packed, blue-staining bacteria. At the base of the valve were found rather large, irregular masses of bacteria, and polymorphonuclear cells. The inflammatory reaction extended for only a short distance along the ventricular endocardium as well as the aortic intima. At the base of the aorta, the intima was markedly thickened and stained palely, containing only a few nuclei. The remainder of the wall consisted of rather dense collagenous fibers, slightly separated from each other. Between them were a few spindle-shaped nuclei. A section stained by Gram's method showed many short, plump, pink-staining rods. In the aorta were found changes of moderate arteriosclerosis. No exudate was found in the alveoli of the lungs. In one area were several large masses of closely packed bacteria. Some of the alveolar walls were densely infiltrated with polymorphonuclear cells. The malpighian corpuscles of the spleen were small. The pulp contained a large

number of red blood cells, small mononuclears and a moderate number of polymorphonuclear cells. Bacterial colonies were also seen. The liver cells were large and stained poorly. Many small and large fat droplets were seen within them, throughout the lobule. At one point beneath the capsule were several large masses of densely packed bacteria. The liver cells about these masses were small and irregular, and stained poorly. There was, however, no polymorphonuclear reaction. The pancreas and suprarenals were normal. In the latter in a group of small vessels were found closely packed masses of bacteria. In the kidney, numerous glomeruli were completely hyalinized. The capsules of some of the glomeruli were thickened. The cells of the tubules were large, and stained palely. Between the tubules, numerous mononuclear cells were seen. In one of the collecting tubules was a large mass of bacteria. The interstitial tissue near it was densely infiltrated with small mononuclear cells. At one point there was rather extensive hemorrhage with necrosis of the tubules in the adjacent areas. In one section, a rather large infarct was present. At one point were several masses of bacteria surrounded by a collection of polymorphonuclear cells. The tubules in the adjacent areas appeared necrotic, and were separated from each other by edema and hemorrhage. The sections of the pelvic organs were normal. The section of the duodenum and gallbladder showed that the epithelial lining of the duodenum was missing. Brunner's glands were normal. The lymphatic vessels of the submucosa were distended, and within the muscular coats were numerous large collections of small lymphocytes. Binding the wall of the duodenum to the external wall of the gallbladder was a very dense band of connective tissue. In the latter were numerous lymphatics dilated with plugs of bacteria. Within it also were several accumulations of small mononuclear cells. The muscle layers of the gallbladder were separated by edematous newly formed connective tissue as well as by an infiltration of small mononuclear cells. The submucosa of the gallbladder was slightly edematous. At some points there was extensive hemorrhage, edema and necrosis of tissue. The lining epithelial cells were not present.

The anatomic diagnosis was cholelithiasis, with calculi in the gallbladder and cystic duct, acute gangrenous cholecystitis (*Bact. acidilactici*), acute endocarditis of the aortic valve (*Bact. acidilactici*), bacteremia (*Bact. acidilactici*), infarct of the left kidney, acute splenic tumor, a fatty liver, and fibrous peritoneal adhesions.

COMMENT

Jacob,¹¹ in his nine cases of *Bact. coli* sepsis, found the original focus to be in the biliary passages, the urinary tract, the gastro-intestinal tract or the female genital tract. In forty-nine cases, Brian¹³ found the biliary tract to be the focus in sixteen instances, the urinary tract in thirteen, the intestinal tract in twelve, and the female genital tract in nine. Felty and Keefer¹⁴ reported the urinary tract to be the portal of entry in sixteen cases of twenty-eight, twelve of these occurred in males. They had no case originating in the biliary tract. They also

13 Brian, O. Ueber Allgemeininfektion durch *Bacterium coli commune* (*Coli-sepsis*), *Deutsches Arch. f. klin. Med.* **106** 379, 1912.

14 Felty, A. R., and Keefer, C. S. *Bacillus Coli Sepsis*. Clinical Study of Twenty-Eight Cases of Blood Stream Infection by Colon Bacillus, *J. A. M. A.* **82** 1430 (May 3) 1924.

found that the colon bacillus does not tend to invade the blood spontaneously, but usually follows cystoscopy or surgical trauma. This happened in twenty of the twenty-eight cases. When sepsis occurs, the local lesion is usually extensive. Libman¹⁵ stated that "acute bacterial endocarditis arises secondarily to active purulent foci." In his experience, the colon bacillus enters the blood by way of the genito-urinary tract, uterus or gallbladder. The bacteremia or pyelonephritis due to *Bact coli* or *Bact mucosum-capsulatum* follows genito-urinary manipulation.

The original focus of infection in case 1 was most probably the prostate gland. The biliary tract can be safely ruled out as the original source, since the lesions in the gallbladder were chronic in character, and there were no active lesions. The focus in the second case, however, was definitely in the gallbladder. The points of similarity between these cases and those of *Bact coli* sepsis can be brought out by comparison.

In the first case, the patient showed no signs of heart involvement when he entered the hospital. Following the opening of the abscess there was invasion of the blood stream by the organism since the blood culture showed the presence of a gram-negative bacillus two days later. The highest leukocyte count was obtained at this time. His temperature began to drop after this, and nine days later the blood culture was sterile. His temperature then indicated renewal of the sepsis, and a heart murmur was heard which became louder from day to day. The blood culture again showed the presence of *Bact acidilactici*. This may well be interpreted as indicating the invasion of the blood following surgical trauma, with localization of the bacilli on the aortic valve leaflets.

Repeated blood cultures after this showed the presence of *Bact acidilactici*. The final changes were due to detachment of tiny bits of vegetation which gave rise to the petechiae in the skin, the milium purulent foci in the viscera and the bacterial plugs in the vessels. The second peak of leukocytosis was obtained at this time.

In the second case, the focus was undoubtedly in the gallbladder. Though the history is inadequate, the "attack" that was described as occurring eighteen months before admission might well have been one of acute cholecystitis, superimposed on chronic cholecystitis with stone formation. The causative organism is not known. This acute attack subsided and healed, with the formation of adhesions between the gallbladder and duodenum. Another acute attack occurred shortly before admission. The causative organism again is not known. It is possible that the *Bact acidilactici* reached the gallbladder from the loop of duodenum which was adherent, or that it was the primary cause of the infection. The establishment of a purulent focus in the gallbladder was

¹⁵ Libman, E. General Infections by Bacteria, J. Michigan M. Soc. **23** 462, 1924.

followed by sepsis and the coincident infection of the aortic valve. With the subsidence of the sepsis, which is usually of short duration,¹³ there was a period of two weeks during which the patient was symptom-free. Following the formation of the vegetation, sepsis was renewed and the valve became the important source for dissemination of the organism, because of the emboli that became detached.

There is one point of resemblance in these two cases of *Bact. acidilactici* endocarditis that may be important or merely a coincidence. The aortic valve leaflets were the site of the vegetation formation. A single case of *Bact. coli* sepsis with endocarditis in the Presbyterian Hospital records also shows involvement of the aortic valve. The case of *Bact. coli* endocarditis reported by Horder⁷ showed at autopsy large, lumpy, friable, easily detached vegetations on the aortic valve.

SUMMARY

Two cases of *Bact. acidilactici* endocarditis, closely resembling cases of infection with *Bact. coli*, are reported because of their rarity. More complete bacteriologic studies of cases of *Bact. coli* sepsis will undoubtedly bring to light more examples of *Bact. acidilactici* infections. The coincidence of aortic valve involvement in two cases of *Bact. acidilactici* endocarditis and in two cases of *Bact. coli* endocarditis is pointed out.

EFFECT OF HISTAMINE ON ALKALI RESERVE AND ON BLOOD SUGAR IN MAN

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Histamine, β -imidazolyethylamine, is a decomposition product of albumin and is derived from the amino-acid histidine by the splitting off of carbon dioxide. It is exceedingly active both pharmacologically and physiologically, and has therefore been widely studied.

The action of histamine on the secretory function of the stomach was proved in animal experimentation by Popielski,¹ Keeton, Koch and Luckhardt² and others. On the human stomach its effect was first observed in 1922 by Carnot, Koskowski and Liebert,³ and since that time it has been the subject of numerous investigations. Matheson and Ammon,⁴ Gompertz and Vorhaus,⁵ Andresen,⁶ Bockus and Bank,⁷

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2 Keeton, R W, Koch, F C, and Luckhardt, A B. Gastrin Studies III. The Response of the Stomach Mucosa of Various Animals to Gastrin Bodies, *Am J Physiol* **51** 454, 1920

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4 Matheson, A K, and Ammon, S E. Observations on the Effect of Histamine on the Human Gastric Secretion, *Lancet* **1** 482, 1923

5 Gompertz, L M, and Vorhaus, M G. Studies on the Action of Histamine on Human Gastric Secretion, *J Lab & Clin Med* **11** 14, 1925

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7 Bockus, H L, and Bank, J. The Value of Histamine as a Test for Gastric Function, *Arch Int Med* **39**:508 (April) 1927

Katzenelbogen and Choisy,⁸ Bloomfield and Polland,⁹ Fenyès¹⁰ and Henning¹¹ demonstrated that histamine injected either subcutaneously or intramuscularly is a most reliable stimulant for gastric secretion, especially the secretion of free hydrochloric acid, and that the secretion of hydrochloric acid occurs within fifteen minutes after the injection of histamine, usually reaching a maximum in about from thirty to sixty minutes.

Because of the increase in the acidity of the stomach secretion, Katzenelbogen¹² reasoned that a corresponding general decrease of acidity should take place in all other body fluids. This hypothesis was apparently confirmed at least in part by his experimental study on rabbits. He observed that sixty minutes after the intramuscular injection of 1 cc of a 1:1,000 histamine solution there was an increase of the alkali reserve from 22.2 to 105 per cent, or an average of 50.55 per cent. On the basis of these results and on the assumption that histamine increases the alkali reserve by draining acidity into the stomach, he suggested that it might be of value in the treatment for nondiabetic acidosis, especially if combined with the parallel elimination of the acidity either by the removal of the stomach contents or by neutralization with alkali given by mouth. As to its use in diabetic acidosis and coma, he cautioned that histamine, as he and Abramson¹³ and La Barre¹⁴ showed, provokes hyperglycemia. On the other hand, Hiller¹⁵ studied the effect of the subcutaneous injection of histamine on the acid-base balance of normal dogs. The dose varied from 0.1 to 3 mg per kilogram of body weight. She found that from forty to ninety minutes after the injection of the histamine, the p_H of the blood and the bicarbonate of the plasma were both decreased. Corresponding with this change there was an increased excretion of alkali in the urine.

8 Katzenelbogen, S., and Choisy, R. L'influence de l'histamine sur la secretion gastrique, *Arch de mal de l'app digestif* **17** 278, 1927, *Étude de la secretion gastrique par l'épreuve de l'histamine*, *Schweiz med Wchnschr* **57** 1009, 1927.

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14 La Barre, Jean. À propos des variations de la glycémie consecutives à l'injection intraveineuse d'histamine, *Compt rend Soc de biol* **94** 779, 1926.

15 Hiller, A. The Effect of Histamine on the Acid-Base Balance, *J. Biol Chem* **68** 833, 1926.

Boyd, Tweedy and Austin¹⁶ injected 0.7 mg of histamine subcutaneously into dogs weighing from 9 to 12 Kg and observed a rise in the blood p_H amounting to from 0.02 to 0.06, from one to two hours after the injection. With larger doses a decrease in p_H was observed.

TABLE 1—Carbon Dioxide Combining Power of Plasma, Control Experiments

Patient	Time Between Blood Samples, Minutes	Alkali Reserve		
		First Blood Sample, per Cent by Volume	Second Blood Sample, per Cent by Volume	Difference, per Cent by Volume
1	45	56.5	55.5	-1.0
2	45	54.8	53.0	-1.8
3	50	60.2	60.2	None
4	55	57.7	55.8	-1.9
5	60	62.3	59.5	-2.8
6	60	59.3	58.9	+0.4
7	65	54.7	55.1	+0.4
8	65	60.9	61.0	+0.1
9	70	60.4	57.9	-2.5
Average difference				-1.1

TABLE 2—Carbon Dioxide Combining Power of Plasma Before and After the Injection of 0.5 Mg of Histamine

Patient	Time Between Blood Samples, Minutes	Alkali Reserve		
		First Blood Sample, per Cent by Volume	Second Blood Sample, per Cent by Volume	Difference, per Cent by Volume
1	20	66.6	60.0	-6.6
2	25	61.9	61.9	±0.0
3	35	58.5	64.2	+5.7
4	35	68.8	68.8	±0.0
5	40	57.6	65.2	+7.6
6	40	59.0	63.1	+4.1
7	45	56.8	60.5	+3.7
8	45	59.3	63.7	+4.4
9	45	64.1	69.1	+5.0
10	45	63.5	67.5	+4.0
11	50	57.4	57.9	+0.2
12	50	55.5	58.2	+2.7
13	55	60.5	55.3	-5.2
14	60	71.4	68.7	-2.7
15	60	67.8	68.6	+0.8
16	60	54.1	61.6	+7.5
17	60	63.2	65.0	+1.8
18	60	56.5	56.5	±0.0
19	75	71.3	73.2	+1.9
Average difference				+1.8

Because the response of the acid-base balance has been found to vary with (1) the amount of histamine injected, (2) the manner in which it is administered and (3) the species in which the observations are made, we decided to investigate whether a change occurs in the

¹⁶ Boyd, T. E., Tweedy, W. R., and Austin, W. C. Some Effects of Histamine on the Acid-Base Balance, *Proc Soc Exper Biol & Med* **25**:451, 1928.

alkali reserve in man when the dose corresponds to that employed clinically, namely, from 0.5 to 0.75 mg

Further, since Katzenelbogen and Abramson¹³ working with guinea-pigs, Ni¹⁷ working with dogs and Fényes¹⁰ working with human subjects had shown that histamine produces hyperglycemia, it was also decided to investigate its effect on the blood sugar level in man

Our observations were carried out on ward patients in Prof. Alfred Luger's Medical Abteilung of the Kaiserin Elisabeth Hospital in Vienna. Most of the subjects were young adults, all were free from fever and without an obvious disturbance of gastric function

TABLE 3—Carbon Dioxide Combining Power of Plasma Before and After the Injection of 0.75 Mg of Histamine

Patient	Time Between Blood Samples, Minutes	Alkali Reserve		
		First Blood Sample, per Cent by Volume	Second Blood Sample, per Cent by Volume	Difference, per Cent by Volume
1	30	61.3	60.1	-1.2
2	35	64.3	67.6	+3.3
3	35	59.8	62.1	+2.3
4	40	57.4	54.3	-3.1
5	45	67.7	68.7	+1.0
6	50	62.3	62.3	None
7	50	64.6	64.1	-0.5
8	50	64.5	64.7	+0.2
9	50	60.8	62.8	+2.0
10	50	69.3	59.3	None
11	50	60.8	61.8	+1.0
12	55	60.7	71.2	+10.5
13	55	52.2	45.4	-6.8
14	55	62.3	62.3	None
15	55	56.5	58.8	+2.3
16	60	60.0	57.7	-2.3
17	60	66.1	67.6	+1.5
18	75	56.2	55.9	-0.3
Average difference				+0.55

TECHNIC

All subjects were fasting and at rest in bed, they received no food or drink between the blood takings. The experiments were carried on between the hours of 8 and 10 a. m. In every case in which histamine was used, it was given in 1:1,000 solution so that 1 cc contained 1 mg. Ten cubic centimeters of blood was taken from an arm vein into a tube containing a small amount (0.05 Gm.) of potassium oxalate and under paraffin oil before and from twenty to seventy-five minutes after the intramuscular or subcutaneous (gluteal) injection of histamine. The specimens were immediately centrifugated, after which approximately 3 cc. of plasma was pipetted off, placed in a separatory funnel and saturated with alveolar air. The plasma carbon dioxide combining power was then determined by the direct method of Van Slyke and Cullen. For the blood sugar determination, speci-

17. Ni T. G. On the Inverse Change Between the Concentration of Glucose and Chloride in the Blood, *Am. J. Physiol.* 78:158, 1926

mens were taken in duplicate from an arm vein at the same time as for the alkali reserve. The micromethod of Bang was employed, the average of the two determinations being given in the accompanying tables. Seventy patients were used for this study, and although one hundred cases are presented in our tables, this apparent discrepancy is due to the fact that parallel blood sugar and alkali reserve determinations were made in thirty cases.

RESULTS

In table 1 are presented nine cases used as controls. The figures show very little variation in the alkali reserve in from forty-five to

TABLE 4—*Carbon Dioxide Combining Power of Plasma Before and Sixty Minutes After 2 Gm of Sodium Bicarbonate by Mouth*

Patient	Alkali Reserve		
	First Blood Sample, per Cent by Volume	Second Blood Sample, per Cent by Volume	Difference, per Cent by Volume
1	60.0	60.6	+0.6
2	59.4	61.8	+2.4
3	64.1	66.5	+2.4
4	63.0	72.4	+9.4
5	59.9	69.1	+9.2
6	64.2	71.2	+7.0
Average increase			+5.17

TABLE 5—*Carbon Dioxide Combining Power of Plasma Before and Sixty Minutes After 2 Gm of Sodium Bicarbonate by Mouth and 0.75 Mg of Histamine Subcutaneously*

Patient	Alkali Reserve		
	First Blood Sample, per Cent by Volume	Second Blood Sample, per Cent by Volume	Difference, per Cent by Volume
1	68.8	75.3	+6.5
2	66.7	71.6	+4.9
3	64.0	73.0	+9.0
4	64.0	71.8	+7.2
5	66.9	76.7	+9.8
6	68.2	73.9	+5.7
Average increase			+7.18

seventy minutes. The average variation is a decrease of 1.1 per cent by volume.

Table 2 shows the results in nineteen cases from twenty to seventy-five minutes after the intramuscular injection of 0.5 mg of histamine. A small increase is noted in thirteen cases, a decrease in three and no change in three. The average variation was an increase of 1.8 per cent by volume.

In table 3 are shown the figures in eighteen cases after the intramuscular injection of 0.75 mg of histamine. A small increase in the alkali reserve occurred in nine cases and in one case an increase of

10.5 per cent by volume. There was a decrease in six cases and no change in three. The average was an increase of only 0.55 per cent by volume.

We then tried giving alkali by mouth in the form of sodium bicarbonate in an attempt thereby to neutralize hyperacidity of the gastric contents, and to prevent, if possible, the reabsorption of the acid. The results are seen in tables 4 and 5. The patients in the six cases in table

TABLE 6—*Carbon Dioxide Combining Power of Plasma Before and After 2 Gm of Tribasic Calcium Phosphate by Mouth*

Patient	Alkali Reserve		
	First Blood Sample, per Cent by Volume	Second Blood Sample, per Cent by Volume	Difference, per Cent by Volume
1	61.9	61.7	-0.2
2	63.7	63.7	None
3	61.2	62.1	+0.9
4	55.4	54.6	-0.8
5	51.6	51.6	None
6	59.1	61.0	+1.9
Average increase			+0.3

TABLE 7—*Carbon Dioxide Combining Power of Plasma Before and After 2 Gm of Tribasic Calcium Phosphate by Mouth and the Injection of 0.5 Mg of Histamine Subcutaneously*

Patient	Alkali Reserve		
	First Blood Sample, per Cent by Volume	Second Blood Sample, per Cent by Volume	Difference, per Cent by Volume
1	58.4	61.9	+3.5
2	59.8	57.5	-2.3
3	68.7	73.1	+4.4
4	59.3	62.0	+2.7
5	61.2	65.9	+4.7
6	59.2	61.6	+2.4
Average increase			+2.6

4 used as controls were given 2 Gm of sodium bicarbonate by mouth. In the second group (table 5) the six patients were given 2 Gm of sodium bicarbonate and 0.5 mg of histamine subcutaneously. An increase in the alkali reserve occurred in every case in both groups. The average increase in the controls was 5.17 per cent by volume, while the average in the group that received both alkali and histamine was somewhat greater, namely, 7.18 per cent by volume.

Mindful of the objection that might be raised that the increase in the alkali reserve was due to the absorption of the sodium bicarbonate, we decided to give tribasic calcium phosphate, which neutralizes the

acidity of the gastric secretion without producing an alkaline solution¹⁸ Six patients were given 2 Gm of this alkali by mouth, and six received in addition 0.5 mg of histamine subcutaneously Tribasic calcium phosphate alone gave a small increase of 0.3 per cent by volume, while when combined with histamine the average increase was still only 2.6 per cent by volume

In table 8 are listed the cases of six patients used as controls for blood sugar determinations The variations range from an increase of

TABLE 8—*Blood Sugar in Milligrams per Hundred Cubic Centimeters, Control Experiments*

Patient	Time Between Blood Samples, Minutes	First Blood Sample	Second Blood Sample	Difference
1	45	105.5	102.0	-3.5
2	45	107.0	100.0	-7.0
3	50	112.0	104.0	-8.0
4	55	97.0	98.5	+1.5
5	60	108.5	110.0	+1.5
6	50	104.0	101.0	-3.0
Average difference				-3.1

TABLE 9—*Blood Sugar in Milligrams per Hundred Cubic Centimeters Before and After the Intramuscular Injection of 0.5 Mg of Histamine*

Patient	Time Between Blood Samples, Minutes	First Blood Sample	Second Blood Sample	Difference
1	20	92.5	94.0	+1.5
2	25	118.5	115.5	-3.0
3	35	112.0	107.0	-5.0
4	35	107.0	114.0	+7.0
5	40	121.0	128.0	+7.0
6	40	116.0	124.0	+8.0
7	45	121.0	121.0	None
8	50	114.0	110.0	-4.0
9	50	121.0	119.5	-1.5
10	55	118.0	114.0	-4.0
11	60	107.0	107.0	None
12	75	120.0	120.0	None
Average difference				+0.50

1.5 mg per hundred cubic centimeters to a fall of 8 mg, the average variation being a fall of 3 mg in from forty-five to sixty minutes

In table 9 are presented twelve cases, showing the blood sugar in milligrams per hundred cubic centimeters from twenty to seventy-five minutes after the intramuscular injection of 0.5 mg of histamine The results varied, with an increase in four cases, a decrease in five and no change in three, the average variation being an increase of 0.5 mg per hundred cubic centimeters

In table 10 are listed the results in twelve cases in from thirty to seventy-five minutes after the intramuscular injection of 0.75 mg of

¹⁸ Hiller (footnote 15) Boyd, Tweedy and Austin (footnote 16)

histamine As in table 9, no definite, uniform effect occurred There was an increase in four cases, a fall in seven and no change in one The average difference was an increase of 1.25 mg per hundred cubic centimeters

COMMENT

From our results it is evident that the intramuscular injection of histamine does not produce a uniform and significant increase either in the alkali reserve or in the blood sugar While it is true that a small increase in the carbon dioxide combining power of the blood plasma did occur in most of the cases after the injection of histamine, it was not of sufficient degree to encourage the use of histamine as a therapeutic agent in acidosis We are unable to explain why more cases showed an

TABLE 10—*Blood Sugar in Milligrams per Hundred Cubic Centimeters Before and After the Intramuscular Injection of 0.75 Mg of Histamine*

Patient	Time Between Blood Samples, Minutes	First Blood Sample	Second Blood Sample	Difference
1	30	100.0	97.0	-3.0
2	35	95.5	100.0	+4.5
3	35	104.0	112.0	+8.0
4	40	116.0	110.0	-6.0
5	45	15.5	89.0	-6.5
6	50	102.0	102.0	None
7	50	104.0	102.0	-2.0
8	50	107.0	105.5	-1.5
9	60	97.0	98.5	+1.5
10	60	110.0	105.5	-4.5
11	60	113.5	110.0	-3.5
12	75	99.5	101.5	+2.0
Average difference				+1.25

increase after the smaller dose of 0.5 mg of histamine than after the injection of 0.75 mg, the slight difference, however, is insignificant

The combined administration of sodium bicarbonate by mouth and 0.75 mg of histamine subcutaneously does produce a uniform and fairly significant increase in the alkali reserve This increase is not significantly greater than that produced by sodium bicarbonate alone

Trisbasic calcium phosphate alone caused no appreciable increase in the alkali reserve, combined with the subcutaneous administration of histamine, a slight increase occurred

That the pouring forth of hydrochloric acid in the stomach following the injection of histamine does not result in a decrease in the acidity of all other body fluids is now known Matzner and Gray¹⁹ have reported that histamine produces an increased secretion of bile and alkaline intestinal juices Also they found that no more than 50 per

¹⁹ Matzner, M, and Gray, I The Comparative Changes in the Gastric Acidity and Urinary Reaction After the Injection of Histamine, Arch Int Med 47:202 (Feb) 1931

cent of the patients, in whose gastric contents free hydrochloric acid was demonstrated after the subcutaneous injection of histamine, had a definite alkaline reaction in the urine. Further, Neale and Klumpp,²⁰ working with children of different ages, found that following the injection of histamine there occurred an increase in the alkalinity of the duodenal contents accompanying the secretion of acid in the stomach.

While a few cases showed a small increase in the blood sugar after the injection of histamine, the average change was slight.

CONCLUSIONS

1 The intramuscular injection of from 0.5 to 0.75 mg. of histamine usually produces a small increase in the alkaline reserve in man. The increase, however, is not sufficient to warrant its therapeutic application in acidosis.

2 The combined administration of sodium bicarbonate by mouth and histamine subcutaneously produces a significant increase in the alkali reserve, but the increase is not significantly greater than that produced by the alkali alone. Tribasic calcium phosphate alone or combined with histamine increases the alkali reserve only slightly.

3 The intramuscular injection of from 0.5 to 0.75 mg. of histamine does not produce a significant increase in the blood sugar level in man.

Prof. Alfred Luger gave many helpful suggestions and permitted us to use his cases in the Kaiserin Elisabeth Spital, Vienna, Austria.

²⁰ Neale, A. V., and Klumpp, T. G. Action of Histamine on the Pancreas, *J. Clin. Investigation* 9:197, 1930.

EFFECT OF QUINIDINE SULPHATE IN INHIBITING VENTRICULAR FIBRILLATION

AN EXPERIMENTAL STUDY

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It has been quite definitely established that quinidine prolongs the refractory period of heart muscle, this has been regarded as the mechanism by which quinidine stops conditions due to circus movement of the heart such as auricular flutter and fibrillation. From clinical experience it has also been known that repeated administration of quinidine by mouth prevents the inception of these disturbances in the auricle which otherwise would be recurring in transient form¹. Because fibrillation of the ventricles is also regarded as due to a circus movement, a similar method of therapy might become available as a preventive measure. Morawitz,² on empiric grounds, successfully used the drug as a prophylactic agent in patients whom he regarded as liable to sudden cardiac death, his figures showed a distinct diminution in the number of sudden deaths under the quinidine regimen. It is the general opinion at the present time that ventricular fibrillation is responsible for many cases of sudden cardiac death³. Stepp and Parade⁴ and Weber⁵ likewise advocated cautious quinidine medication, which they believe prevents or postpones the sudden fatal outcome.

On the other hand, some investigators reported that quinidine may tend to favor the inception of ventricular fibrillation. Kerr and Bender⁶

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From the Laboratories of Physiology in the Harvard Medical School

1 Bramwell, J C, and Ellis, R. The Ultimate Results of Quinidine Therapy in Auricular Fibrillation, *Lancet* **2** 960 (Nov 10) 1928

2 Morawitz, P, and Hochrein, M. Zur Verhütung des akuten Herztodes, *München med Wchnschr* **76** 1075, 1929

3 Hering, H E. Der Sekundenherztod, Berlin, Julius Springer, 1917

4 Stepp, W, and Parade, G W. Untersuchungen und Betrachtungen über den plötzlichen Herztod durch Kammer-Flimmern, *München med Wchnschr* **75** 1869, 1928

5 Weber, A. Ueber den plötzlichen Herztod *Klin Wchnschr* **6** 2458, 1927 (See also footnote 19)

6 Kerr, W J, and Bender, W L. Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulphate Therapy, *Heart* **9** 269, 1922 (See also footnote 18)

reported the occurrence of paroxysmal ventricular fibrillation with recovery, in a case of auricular fibrillation and complete heart block, during quinidine sulphate therapy. They raise the question whether the quinidine was responsible for the ventricular fibrillation. Drury, Horsfall and Munly⁷ found that in dogs ventricular fibrillation was occasionally produced by quinidine. They attributed these anomalous results either to the mode of stimulation employed (slow rhythmic shocks rather than the faradic current) or to the low degree of poisoning produced by the drug. In experiments in which larger doses of quinidine were used and in which the faradic current was employed, they found that fibrillation was produced with difficulty if at all. It is suggested that a dose of the drug, which produces a greater effect in prolonging conduction time than in prolonging the refractory period, might well induce or perpetuate ventricular fibrillation rather than prevent or terminate it.

The purpose of the present research was to obtain definite experimental evidence regarding the effect of quinidine on the ease of elicitation of ventricular fibrillation, and establish a rational basis for its use as a preventive of such a disturbance. Drury, Horsfall and Munly⁷ showed that quinidine has the same effect on ventricular muscle that it has on heart muscle as a whole and on auricular muscle, that is to say, it lengthens the absolute refractory period and reduces the rate of conduction. Hecht and Rothberger⁸ found that under quinine the ventricle of the cat's heart is thrown into fibrillation with difficulty or not at all, they made no similar study of quinidine.

EXPERIMENTAL METHOD

Since the cat's heart presents the advantage of recovering spontaneously from ventricular fibrillation,⁹ cats were used in these experiments. The cat's heart can be stimulated repeatedly, and repeated determination of a "threshold" current for fibrillation can be made.

In the first experiments ethyl carbamate (urethane) anesthesia was employed. In the later series the animals were decerebrated by the method described by Cannon and Britton.¹⁰ A stylet is driven swiftly through the thin petrous portion

7 Drury, A. N., Horsfall, W. N., and Munly, W. C. Observations Relating to the Action of Quinidine Upon the Dog's Heart. The Refractory Period of, and Conduction in, Ventricular Muscle, *Heart* **9** 365, 1922.

8 Hecht, A. V., and Rothberger, C. J. Experimentelle Beiträge zur Kenntnis der Chininwirkung bei Herzflimmern, *Ztschr. f. d. ges. exper. Med.* **7** 134, 1919.

9 Porter, W. T. The Recovery of the Heart from Fibrillary Contractions, *Am. J. Physiol.* **1** 71, 1898. d'Halluin, M. Le massage du coeur, *Presse med.* **12** 345, 1904. MacWilliam, J. A. Fibrillar Contraction of the Heart, *J. Physiol.* **8** 296, 1887.

10 Cannon, W. B., and Britton, S. W. Studies on the Conditions of Activity in Endocrine Glands. XV. Pseudoeffective Medulladrenal Secretion, *Am. J. Physiol.* **72** 286, 1925.

of the temporal bone about 1 cm above the external auditory meatus with a quick blow of a hammer (no anesthesia having been administered), and on reaching the opposite bony wall, the tip of the styllet is immediately drawn across the floor of the skull with a single rapid stroke, thus disconnecting the cerebral peduncles from the brain stem. The animal at once goes into decerebrate rigidity and survives in this condition for several hours. The trachea is then cannulated and artificial respiration begun.

The heart is exposed *in situ*, and the pericardium sewed to the thoracic wall by a modification of the Drinker technique.¹¹ The heart can then be inspected directly. Fibrillation is produced by stimulating the heart directly with a bipolar stimulating electrode attached to the secondary coil of a large inductorium. The secondary coil is closely coupled to the primary and the current in the primary coil is varied by means of a rheostat, the current in the secondary coil varies directly with that in the primary and not logarithmically as it would if the current were varied by changing the distance between the two coils. An interruptor and an ammeter are included in the primary circuit. The heart is stimulated in the same spot each time, in the later experiments wire electrodes were sewed directly into the ventricular wall so that no variation in the site of stimulation was possible. The stimulation is applied for the same length of time on each occasion, five seconds unless otherwise stated. The cat is maintained at constant temperature and the exposed heart is kept moist with 0.9 per cent saline at body temperature.

The heart is stimulated with gradually increasing strengths of current, with intervals between stimulation adequate for the heart to recover, until the strength of current at which persistent fibrillation is produced has been determined. This current is called the threshold for ventricular fibrillation. At currents below this value the heart either is unaffected, is accelerated, or goes into fibrillation only while the current is being applied. This latter condition has been called "pseudofibrillation."¹² In true fibrillation a mechanism of circulating excitation is established, whereas in pseudofibrillation this is not so. With some exceptions stimulation with currents above the threshold value produces persistent fibrillation, while subthreshold currents cause, at the most, pseudofibrillation. In several experiments, however, it was found that currents above the strength which was first believed to be the "threshold" current, did not produce true fibrillation and, conversely, that currents below that value did produce persistent fibrillation, despite all efforts to preserve identical conditions. (Experiments in which it was impossible to check the thresholds by redetermination have been excluded from the tabulations.) Most observers have not reported such anomalous results but apparently have been content to designate as the threshold the first strength of current at which fibrillation is produced, working up gradually from weaker currents. The present research seems to show that although this value generally is the true threshold it is not always so. The production of persistent fibrillation appears to be the result of changes in other variables than the amperage of the applied current, such as the site of stimulation,¹³ the temperature of the heart,¹⁴ exhaustion,¹⁴ asphyxia, etc.

11 Drinker, C. K. A Useful Heart Method, *J. Exper. Med.* **33** 675, 1921.

12 MacWilliam, J. A. The Mechanism and Control of Fibrillation in the Mammalian Heart, *Proc. Roy. Soc. London, s. B.* **90** 302, 1917-1919.

13 Braun, L., and Samet, B. Experimentelle Untersuchungen an den Koronargefassen und uber Kammerflimmern (Zur Prophylaxe des Flimmerns), *Wien klin. Wchnschr.* **44** 136, 1931.

14 MacWilliam (footnote 9).

Once true fibrillation is produced, the heart may recover spontaneously after a so-called "postundulatory pause"¹⁵ In the event that the heart does not recover of itself, remedial measures such as rhythmic compression of the ventricles (so-called "cardiac massage")¹⁶ or the intracardiac injection of a very weak solution of epinephrine (0.1 cc 1:10,000—1:5,000) may prove effective When the depressed heart is massaged, the spontaneous beat develops more readily during a pause One can count on successful resuscitation by massage only as long as the heart possesses a certain tone, that is, while there still remains a sense of firmness Once the heart muscle is weak and flaccid, massage is of no avail The resuscitatory efforts are not always successful, particularly with heavier cats, and many of the experiments ended with the determination of but one threshold

EXPERIMENTAL RESULTS

In the first set of experiments the threshold current was first determined for the normal or unquinidized animal, then the threshold

TABLE 1—*Effect of the Absorption of Quinidine in Causing a Rise in the Threshold for Ventricular Fibrillation*

Exper No	Date	Weight, Kg	Anesthesia	Threshold Before Quinidine	Threshold After Quinidine
1	2/18/30	2.3	Ethyl carbamate	11.77 cm. between coils	8.38 cm. between coils
2	4/ 9/30	2.3	Ethyl carbamate	0.30 amperes or less	0.43 amperes
3	7/22/30	2.3	Ethyl carbamate	0.25 amperes	0.35 amperes
4	7/23/30	2.8	Ethyl carbamate	0.35 amperes	0.40 amperes
5	7/24/30	3.5	Ethyl carbamate	0.20 amperes	0.30 amperes
6	7/25/30	2.7	Ethyl carbamate	0.35 amperes	0.55 amperes
7	7/28/30	1.7	Ethyl carbamate	0.30 amperes	1.50 amperes†
8	7/29/30	1.9	Ethyl carbamate	0.15 amperes	0.50 amperes
9	8/ 1/30	3.3	Ethyl carbamate	0.30 amperes	1.50 amperes
10	8/ 3/30	1.5	Ethyl carbamate	0.35 amperes	0.60 amperes or higher
11	9/25/30	1.9	Ethyl carbamate	0.05 amperes or less	1.50 amperes
12	10/30/30	1.6	Ethyl carbamate	0.10 amperes	0.15 amperes
13	11/24/30	1.8	Ethyl carbamate	0.15 amperes	0.30 amperes
14	2/10/31	2.4	Decerebrate	0.05 amperes or less	0.15 amperes
15	2/12/31	2.1	Decerebrate	0.10 amperes	0.15 amperes
16	2/26/31	2.9	Decerebrate	0.10 amperes	0.20 amperes
17	6/ 6/31	2.7	Decerebrate	0.20 amperes	1.50 amperes
18*	6/29/31	3.1	Decerebrate	0.10 amperes	0.30 amperes
Average				0.20 amperes	0.60 amperes

* Heart denervated

† Thirty seconds' duration

was determined after the intravenous injection of an adequate dosage of quinidine sulphate The second determination was made in from fifteen to thirty minutes after the injection, to give ample time for the quinidine to distribute itself in the heart muscle The dosage used was from 5 to 10 mg per kilogram of body weight of the cat It did not seem to be material whether the smaller or larger dose was used

In all the experiments of this series, excepting numbers 4, 12 and 15, quinidine sulphate made necessary an appreciably stronger faradic

¹⁵ Winterberg, H, in *Handbuch der Normalen und Pathologischen Physiologie, Herzflimmern und Herzflattern I Blut Zirkulation-Herz*, Berlin, Julius Springer, 1924, vol 7, p 663 MacWilliam (footnote 9)

¹⁶ Levy, A G *Massage of the Fibrillating Ventricles*, Heart 7 175, 1920 MacWilliam (footnote 9)

current in order to cause ventricular fibrillation (table 1) In the three enumerated experiments the change, though slight, was in the direction of a rise in the threshold Excluding the first experiment, the average threshold for the unquinidized animal in the entire group was 0.20 amperes, for the quinidized animal, 0.60 amperes The average for those animals in which ethyl carbamate anesthesia was used (excepting number 1) was 0.23 amperes in the unquinidized condition and 0.67 amperes in the quinidized condition In the last five experiments of the group, in which the cats were pithed, the average before quinidine administration was 0.11 amperes and after quinidine administration 0.42 amperes It is important to note that the threshold apparently bears no relation to the body weight of the cat The average results of the entire group are probably less significant than the comparative results in a single experiment, because the quinidine threshold of one animal may be a lower value than the normal threshold of another For example,

TABLE 2—*Effect of the Excretion of Quinidine in Causing a Fall in the Threshold for Ventricular Fibrillation*

Exper No	Date	Weight, kg	Anesthesia	Threshold After Quinidine	Threshold After Excretion of Quinidine
19	8/11/30	1.3	Ethyl carbamate	0.50 amperes at 11.52	0.11 amperes at 1.34
20	8/12/30	3.6	Ethyl carbamate	0.40 amperes at 11.32	<0.10 amperes at 12.26
21	8/13/30	1.9	Ethyl carbamate	0.40 0.50 amperes at 11.45	0.25 amperes at 12.57
					0.20 amperes at 1.54
					0.25 amperes at 2.57
22	8/14/30	2.7	Ethyl carbamate	0.20 amperes at 11.11	0.15 amperes at 12.00
23	6/18/31	2.5	Decerebrate	1.00 amperes at 12.48	1.00 amperes at 2.30
24	6/29/31	3.1	Decerebrate	0.30 amperes at 11.53	0.05 amperes at 1.02
25	6/30/31	2.6	Decerebrate	>1.50 amperes at 12.06	1.50 amperes at 1.55
Average				0.62 amperes	0.44 amperes

cats 4, 6 and 10 had normal thresholds of 0.35 amperes while cats 5 and 13 each had quinidine thresholds of 0.30 amperes

In order to rule out the possibility that the previous treatment and manipulation of the heart was the cause of the rise of threshold, it was decided to reverse the procedure used in the first set of experiments The quinidine was given first and the threshold determined after allowing adequate time for absorption An hour or more later the threshold was again determined, when a good part of the quinidine had presumably been excreted

With the exception of experiment 23, all the experiments in this series (table 2) show a fall in the threshold after sufficient time has been allowed to elapse for the quinidine to be excreted in whole or in part Here, again, too much significance must not be given average results It is noteworthy, however, that the average threshold for the quinidized animals in this series was 0.62 amperes, which is approximately the same as the average of the first series, i. e., 0.60 amperes The average after the excretion of the quinidine was 0.44 amperes

This shows that the change in the threshold in the experiments is due to the quinidine and not to extraneous factors such as fatigue and manipulation

In a third series of experiments the methods of the two previous sets were combined (table 3) The threshold was determined thrice, before, shortly after and a longer time after the injection of quinidine With the exception of cat 28, in which quinidine was without effect, the administration of the drug was followed by a rise in the threshold current for ventricular fibrillation and then, with the passage of more time, by a fall in the threshold toward the original level

TABLE 3—*Effect of Absorption and Excretion of Quinidine in Causing a Rise and Fall in the Threshold for Ventricular Fibrillation*

Exper No	Date	Weight, Kg	Anesthesia	Threshold Before Quinidine	Threshold After Quinidine	Threshold After Excretion of Quinidine
26	10/21/30	1.3	Ethylcarbamate	0.20 amperes at 3.42	0.60 amperes at 4.33	0.40 amperes at 5.35 0.30 amperes at 6.29
27	10/23/30	2.2	Ethylcarbamate	0.10 amperes at 3.36	0.20 amperes at 4.17	0.10 amperes at 5.02 (questionable figure)
28	2/16/31	2.3	Decerebrate	0.10 amperes at 2.59	0.10 amperes at 3.41	0.10 amperes at 4.08
29	4/ 8/31	2.4	Decerebrate	0.10 amperes at 10.40	0.40 amperes at 11.28	0.10 0.15 amperes at 12.21
30	6/ 3/31	2.2	Decerebrate	0.05 amperes at 11.13	0.10 amperes at 11.44	0.05 amperes at 12.37
31	6/ 5/31	2.5	Decerebrate	0.05 amperes at 11.38	0.20 0.30 amperes at 12.23	0.10 amperes at 1.34
32	6/30/31	2.6	Decerebrate	0.10 amperes at 2.28	1.50 amperes at 3.19	0.20 amperes at 4.06
Average				0.10 amperes	0.45 amperes	0.14+ amperes

Control experiments (table 4) were performed showing that there is no natural change or only a very slight change in the threshold for ventricular fibrillation during a period of two hours if no quinidine is given Furthermore, the injection of distilled water or of physiologic solution of sodium chloride did not alter the threshold (experiments 35 and 36)

The work was prompted by the clinical results obtained in the treatment of ventricular tachycardia with quinidine¹⁷ In this regard it was found that the drug not only breaks up the abnormal rhythm but may prevent its return when the condition has a tendency to recur in paroxysms As fibrillation of the ventricles may well have a similar

17 Levine, S. A., and Fulton, M. N. The Effect of Quinidine Sulphate on Ventricular Tachycardia. Clinical Observations, J. A. M. A. **92** 1162 (April 6) 1929

relation to ventricular tachycardia as auricular fibrillation has to auricular flutter, it seemed logical that quinidine might actually inhibit the development of ventricular fibrillation. It is well known that although sudden, instantaneous and unexpected death can occur, especially in coronary thrombosis from rupture of the ventricle or from sudden complete heart block, there are other instances where these two factors are inadequate to explain the mechanism of death. It is because such otherwise unexplained deaths may well be due to ventricular fibrillation that the experiments reported in this study may have a practical application for proper quinidine therapy or for some hope in inhibiting these fatalities.

TABLE 4—*The Constancy of the Threshold with Lime and with the Administration of Control Solutions*

Exper No	Date	Weight Kg	Anesthesia	Determinations				
				First, Amperes	Second, Amperes	Third, Amperes	Fourth, Amperes	Fifth, Amperes
3	7/22/30	2.3	Ethyl carbamate	0.25 at 11 36	0.25 at 11 51	0.25 at 12 04	0.25 at 12 14	
7	7/28/30	1.7	Ethyl carbamate	0.30 at 11 40	0.30 at 11 55	0.30 at 12 10	0.30 at 12 25	0.30 at 12 45
33	4/ 5/30	Small cat	Ethyl carbamate	0.47 at 4 07	0.48 at 4 21			
34	11/ 4/30	2.0	Ethyl carbamate	0.15 at 12 12	0.10 at 1 06			
35	11/ 5/30	1.7	Ethyl carbamate distilled water injected at 11 55	0.10 at 12 16	0.10 at 1 05	0.10 at 1 58		
36	11/ 6/30	1.9	Ethyl carbamate, 3.8 cc saline injected at 11 57	0.10 at 11 55	0.10 at 12 55	0.10 at 1 59		

CONCLUSIONS

In a series of thirty-six experiments performed on cats, it was found that quinidine sulphate definitely inhibited the facility with which ventricular fibrillation could be produced by faradic stimulation. It was also found that this effect could not be attributed to manipulation of the heart and the resulting fatigue of the muscle or to the time consumed in the experiments.

It is suggested that these results offer a rational background for proper quinidine therapy as a method of preventing sudden death in those conditions in which ventricular fibrillation is prone to occur.

NOTE—While this paper was in the hands of the printer, two pertinent articles were called to my attention. In one, Davis and Sprague¹⁸ reported the occurrence of syncopal attacks in a patient with rheumatic

18 Davis, D., and Sprague H. B. Ventricular Fibrillation. Its Relation to Heart Block, *Am Heart J* 4: 559, 1929.

heart disease and auricular fibrillation. Following treatment with quinidine in an attempt to restore normal rhythm, electrocardiograms showed ventricular abnormalities consistent with ventricular fibrillation. In this paper the possible action of quinidine in initiating ventricular fibrillation is discussed. In the other, Dock¹⁹ reported a case of recurrent attacks of syncope occurring over a period of eighteen months, due presumably to ventricular fibrillation. Subsequent quinidine medication prevented these attacks.

19 Dock, W. Transitory Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulphate, *Am Heart J* 4 709, 1929

INTRINSIC REGULATION OF GASTRIC ACIDITY

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The mechanisms concerned in the lowering of gastric acidity following digestion have been the subject of considerable research since Pavlov¹ first noticed the apparent diminution of further secretion of hydrochloric acid when there was an accumulation of that substance within the gastric cavity. Although he did no further work on the subject, he originated the idea of intrinsic control of gastric acidity.

Rosemann² noted that although the concentration of total chloride remained constant, or relatively so, in specimens of gastric content, the acid chloride measured as hydrochloric acid and the neutral chloride measured as sodium chloride varied in inverse proportion. He advanced the hypothesis that as the stimulus to gastric secretion became stronger, the amount of chloride ion secreted as hydrochloric acid became greater, and the amount secreted as neutral chloride became correspondingly less. When the stimulus was absent or less marked, the reverse occurred. Earlier investigators, notably Pfaundler,³ had noticed the increase in neutral chloride late in the digestive cycle when the acid chloride was decreasing, and attributed this rise to neutralization of secreted acid chloride by mucin and alkaline pyloric juices.

Boldyreff,⁴ in 1907, suggested that gastric acidity was self-regulated by regurgitation of alkaline duodenal juices. His classic experiments need not be considered here, they have been confirmed many times by

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1 Pavlov, I P. The Work of the Digestive Glands, ed 2, London, Griffin and Company, 1910

2 Rosemann, R. Beiträge zur Physiologie der Verdauung. I Die Eigenschaften und die Zusammensetzung des durch Scheinfütterung gewonnenen Hundemagensaftes, Arch f d ges Physiol **118** 467 (July) 1907

3 Pfaundler, quoted by MacLean, Hugh, and Griffiths, W J. The Automatic Regulation of Gastric Acidity, J Physiol **66** 356 (Dec) 1928

4 Boldyreff, W. Der Uebertritt des natürlichen Gemisches aus Pankreassaft, Darmsaft und Galle in den Magen, Arch f d ges Physiol **121** 13 (Dec) 1907

Cathcart,⁵ Spencer and his associates,⁶ Bolton and his associates⁷ and others Olch and Elman⁸ recently confirmed the part played by regurgitation, diverting or returning pancreatic juice from or to the duodenum at will with an apparatus devised by Elman and McCaughan⁹ They found that neutralization of an acid test meal was rapid when secretions were present in the duodenum and absent or markedly decreased after the diversion of the secretions

Carlson,¹⁰ Hicks and Visser¹¹ and others assumed that, whereas regurgitation into the stomach is a physiologic phenomenon, it is not the important mechanism in the lowering of gastric acidity Carlson, because of observations made over a period of seven years on a man with an opening made at gastrostomy, considered that the concentration of secreted hydrochloric acid varies Other investigators, notably Foster and Lambert¹² and Lim,¹³ confirmed this observation

Rosemann's² hypothesis was emphasized by the investigations of Katsch and Kalk,¹⁴ Steinitz¹⁵ and others Hansman, Day and Clifton¹⁶ expressed the belief that it is impossible to account for the increase in the concentration of neutral chloride by assuming neutralization of

5 Cathcart, E P Reflux from Intestine to Stomach, *J Physiol* **42** 433 (July) 1911

6 Spencer, W H, Meyer, G P, Rehfuess, M E, and Hawk, P B Gastro-Intestinal Studies XII Direct Evidence of Duodenal Regurgitation and Its Influence upon the Chemistry and Function of the Normal Human Stomach, *Am J Physiol* **39** 459 (Feb) 1916

7 Bolton, Charles, and Goodhart, G W Duodenal Regurgitation into Stomach During Gastric Digestion, *Lancet* **1**:420 (March 4) 1922

8 Olch, I Y, and Elman, Robert Regurgitation of Duodenal Content as Factor in Neutralization of Gastric Acidity, *Proc Soc Exper Biol & Med* **25** 184 (Dec) 1927

9 Elman, Robert, and McCaughan, J M On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of the Total Loss of Pancreatic Juice, *J Exper Med* **45** 561 (March) 1927

10 Carlson, A J Contribution to the Physiology of the Stomach XXI The Secretion of Gastric Juice in Man, *Am J Physiol* **37** 50 (April) 1915

11 Hicks, C J, Jr, and Visser, J W Contributions to the Physiology of the Stomach XXVII The Mechanism of Regurgitation of Duodenal Contents into the Stomach, *Am J Physiol* **39** 1 (Nov) 1915

12 Foster, N B, and Lambert, A V S Some Factors in the Physiology and Pathology of Gastric Secretion, *J Exper Med* **10** 820 (Nov) 1908

13 Lim, R K S On the Relationship Between the Gastric Acid Response and the Basal Secretion of the Stomach, *Am J Physiol* **69** 318 (July) 1924

14 Katsch, G, and Kalk, Heinz Statik und Kinetik des Magenchemismus, *Arch f Verdauungskr* **32** 201, 1923

15 Steinitz, Hermann Die Chlorabscheidung des menschlichen Magens in ihrer Beziehungen zu pathologischen Vorgängen, *Arch f Verdauungskr* **42** 57, 1928

16 Hansman, F S, Day, Emily M, and Clifton, R Gastric Chlorides, Their Origin and Significance, *M J Australia* **2** 6 (July 27) 1927

secreted acid chloride by all the available base in mucin, alkaline pyloric secretions and duodenal juice MacLean and Griffiths¹⁷ were also staunch supporters of this intrinsic mechanism, because of several observations The neutralization of acid test meals may be prompt without evidence of regurgitation, either in staining of gastric content by bile or in discovery of tryptic activity in gastric content, acidity varies in a Pavlov pouch as it does in the intact stomach, although regurgitation into a Pavlov pouch is not possible MacLean and Griffiths maintained that an accumulation of hydrogen ions above a certain level inhibits the further secretion of acid

Baird, Campbell and Hein¹⁸ prevented regurgitation by continuous removal of duodenal content by a suction apparatus, and found test meals to be unaltered McCann¹⁹ used Mann and Williamson's²⁰ method of duodenal drainage for the same purpose and found regulation of the acidity of the gastric content unchanged He attributed reduction in the acidity of the gastric content to the gradual reduction of a high rate of secretion to a low rate, and to the capacity of mucus to combine with acid to form a combined acid and a neutral chloride, the concentration of which rises at the end of digestion

In a comprehensive review of the subject Babkin²¹ stated his belief that the curve of acidity is the net result of several important regulatory factors He considered variation of the concentration of secreted acid, and contributed evidence of its significance He expressed the belief that regurgitation is important and that secretion of neutral chloride plays a part To gastric mucin, saliva and foodstuffs he attributed minor rôles

This work was started primarily to determine the buffering capacity of the gastric juice to acids instilled into gastric pouches It was believed that if the acidity of solutions that had been instilled became reduced, under experimental conditions that precluded the possibility of its being neutralized by food, saliva or regurgitated material, one could assume the existence of intrinsic regulation of gastric acidity By following the titratable acidity and the chloride content within the pouch, one might obtain information regarding the nature of this mechanism

17 MacLean, Hugh and Griffiths, W. J. The Automatic Regulation of Gastric Acidity, *J. Physiol.* **66** 356 (Dec.) 1928

18 Baird, M. McC., Campbell, J. M. H., and Hein, J. R. B. The Importance of Estimating Chlorides in Fractional Test Meal Samples, and Some Experiments with the Duodenal Tube, *Guv's Hosp. Rep.* **74** 23 (Jan.) 1924

19 McCann, J. C. Studies on Control of Acidity of Gastric Juice, *Am. J. Physiol.* **89** 483 (Aug.) 1929

20 Mann, F. C., and Williamson, C. S. The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77** 409 (April) 1923

21 Babkin, B. P. Physiological Factors Determining Acidity of Gastric Juice and of Gastric Contents *Canad. M. A. J.* **17** 36 (Jan.) 1927

METHODS OF INVESTIGATION

Operative procedures were all carried out on dogs under ether anesthesia and with aseptic technic. Pyloric pouches were prepared by a modified Polya type of resection in two stages (figs 1 and 2). Little difficulty was encountered, the pouches readily retained solutions instilled through a Pezzer mushroom retention catheter.

With ordinary Pavlov pouches of the fundus, it was almost impossible to prevent excoriation of the skin, and this difficulty was best obviated by constructing pouches by a modification of Mann and Bollman's²² method of preparing an intestinal fistula.²³ Essentially a loop of resected ileum was employed as a fistulous tract to drain the fundic pouch. Anastomosis of the distal end of the loop to the stomach produces a valvelike effect, which prevents leakage and makes excoriation negligible. The possible objection that the relatively alkaline secretion of the loop might interfere with the experimental procedure by being regurgitated into the pouch was removed by inserting a mushroom retention catheter well within the pouch and exerting traction on it until the mushroom impinged strongly against the somewhat contracted line of the gastro-ileac anastomosis. Results in these animals were in every way comparable to those in which the pouches were attached directly to the abdominal wall.

The animals were trained until they became content to lie on a table for hours without restraint, which to a large degree eliminated any possible psychic interference with secretion. Two series of experiments were done, each on animals with pyloric and fundic pouches, both after fasting and after test meals of 100 Gm of meat and 250 cc of water. In the first series, from 10 to 15 cc of hydrochloric acid of known reaction was instilled into a pouch, and about 1 cc was withdrawn at intervals of half an hour. The reaction of these specimens was determined by the quinhydrone electrode as described by Mann and Bollman. These determinations were done to decide whether readings of reaction were a true index of acidity of the content.

In the second series of experiments fractional specimens of the contents of the pouch were not analyzed. Determinations of changes in reaction and in free, combined and total acidity were made. Hydrochloric acid of known strength (approximately twentieth-normal) was instilled into a pouch and allowed to remain therein for from one to three and a half hours in different experiments, and then was removed. Free and total acidity were determined by titration against tenth-normal sodium hydroxide, and the content of chloride by precipitation with a known amount of silver nitrate and by titration of the excess silver against an equivalent solution of ammonium thiocyanate. Differences in volume were noted as evidence of secretion or possible absorption. These experiments were repeated with sulphuric acid.

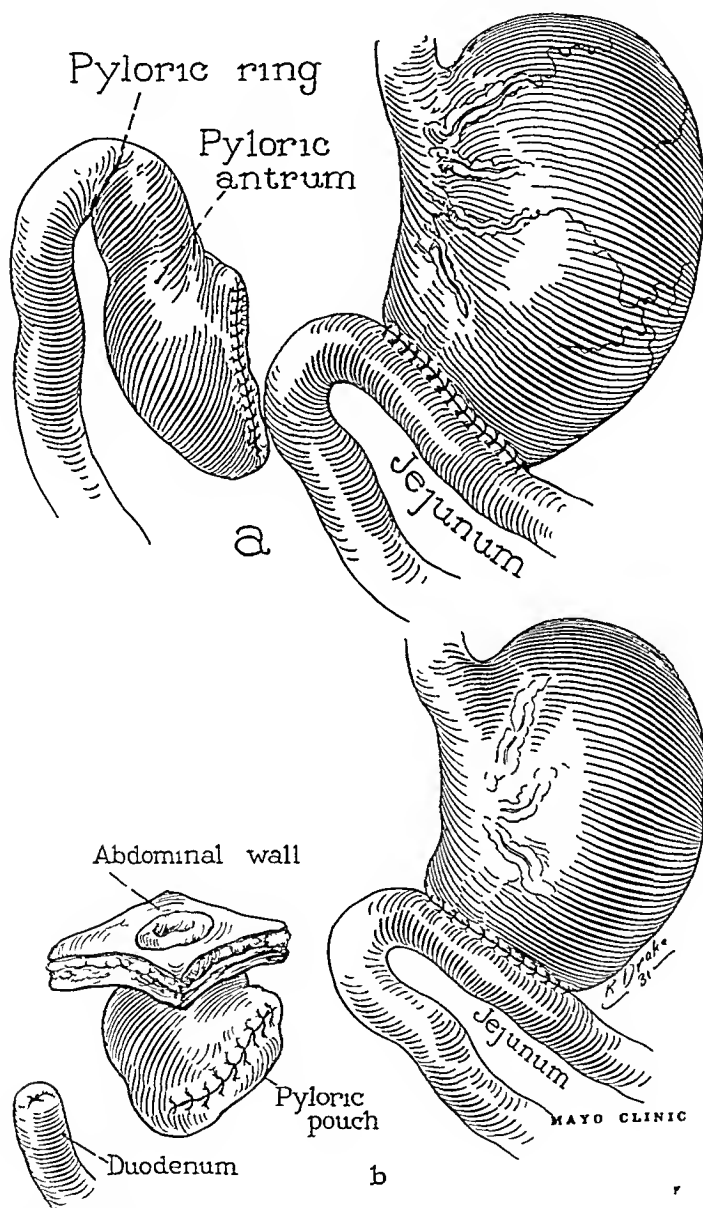
RESULTS

The variations in reaction throughout the first series were not marked. In the pyloric pouches there was a rise in acidity averaging

²² Mann, F. C., and Bollman, J. L. Reaction of Content of Gastro-Intestinal Tract, *J. A. M. A.* **95** 1722 (Dec 6) 1930, A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract, *Ann. Surg.* **85** 794 (March) 1931.

²³ Goldberg, S. L., and Mann, F. C. A Satisfactory Method of Preparing Fundus Gastric Pouches, *Ann. Surg.* **94** 953 (Nov) 1931.

approximately 0.6 of a p_H unit, in the group of animals with fundic pouches the increase was somewhat less (table 1). The second series of experiments was more fruitful. In an experiment in which 10 cc of hydrochloric acid of known strength was injected into a pyloric



The first stage in making a pyloric pouch (after Priestley and Mann) is indicated by *a*, the completed pyloric pouch by *b*.

pouch and allowed to remain for one hour, the chloride content invariably rose, at times 100 per cent or more. The total acidity varied but little, this could be explained adequately by dilution, which at best was not marked. Within an hour, however, about 20 per cent of the free acidity became combined, reaching 40 per cent in some experiments.

(table 2) The same experiments on dogs with fundic pouches gave comparable results (table 3), showing the regulatory mechanism common to both portions of the stomach. In practically every experiment the volume of the content increased, thus showing that secretion into

TABLE 1—*Determinations of the p_H of Samples Removed from Gastric Pouches at Intervals After Instillations of Acid*

	Pyloric Pouch		Fundic Pouch	
	Fasting	After Test Meal	Fasting	After Test Meal
Initial p_H of content of pouch	6.27	6.36	4.73	4.52
p_H of acid instilled*	1.41	1.41	1.64	1.64
p_H of content of pouch				
Thirty minutes later	1.54	1.59	1.71	1.69
One hour later	1.67	1.75	1.75	1.73
One and five tenths hours later	1.75	1.92	1.81	1.75
Two hours later†	2.12	2.12	1.89	1.83

* The amount of acid instilled was 10, 10, 15 and 15 cc, respectively

† The amount of acid recovered was 4, 4, 10 and 13 cc, respectively

TABLE 2—*Changes in 10 Cc of Hydrochloric Acid Instilled into a Pyloric Pouch of a Dog and Removed After One Hour*

	Volume, Cc	Acidity*			Chlorides, Mg for Each 100 Cc	p_H
		Free	Combined	Total		
Fasting						
Acid instilled	10.0	28	0	28	220	1.94
Content removed	11.0	20	5	25	360	2.00
After Feeding						
Acid instilled	10.0	28	0	28	220	1.94
Content removed	11.5	20	5	25	330	2.01

* In all tables acidity is expressed in terms of cubic centimeters of tenth normal sodium hydroxide required to produce end point in 100 cc of content

TABLE 3—*Changes in 10 Cc of Hydrochloric Acid Instilled into a Fundic Pouch of a Dog and Removed After One Hour*

	Volume, Cc	Acidity			Chlorides, Mg for Each 100 Cc	p_H
		Free	Combined	Total		
Fasting						
Acid instilled	10	28	0	28	220	1.94
Content removed	11	20	4	24	450	2.06
After Feeding						
Acid instilled	10	28	0	28	220	1.94
Content removed	12	18	6	24	400	2.02

the pouch had taken place. Feeding had little apparent effect on the results.

All the preceding experiments in the second series were repeated, an approximately twentieth-normal solution of sulphuric acid being used. There was an invariable rise in the chloride content from the initial zero, and changes in acidity were similar to those obtained when hydrochloric acid was used, which is evidence that the presence of a

high enough concentration of hydrogen ions inhibits the secretion of acid by the stomach, regardless of what negative radical it may be linked with (tables 4 and 5)

To determine if possible the extent to which the drop in free acidity would take place, acid was left in pouches for varying periods up to three and a half hours. In an experiment performed after feeding an

TABLE 4—*Changes in 10 Cc of Sulphuric Acid Instilled into a Pyloric Pouch of a Dog and Removed After One Hour*

	Volume, Cc	Acidity			Chlorides, Mg for Each 100 Cc	pH
		Free	Com bined	Total		
Fasting						
Acid instilled	10	50	0	50		1.97
Content removed	11	40	5	45	220	2.12
After Feeding						
Acid instilled	10	50	0	50		1.97
Content removed	12	36	8	44	220	2.21

TABLE 5—*Changes in 10 Cc of Sulphuric Acid Instilled into a Fundic Pouch of a Dog and Removed After One Hour*

	Volume, Cc	Acidity			Chlorides, Mg for Each 100 Cc	pH
		Free	Com bined	Total		
Fasting						
Acid instilled	10	50	0	50		2.02
Content removed	11	32	12	44	180	2.11
After Feeding						
Acid instilled	10	50	0	50		2.02
Content removed	13	26	12	38	220	2.12

TABLE 6—*Changes in 10 Cc of Hydrochloric Acid Instilled into a Fundic Pouch of a Dog After Feeding and Removed After Three and One-Half Hours**

	Volume Cc	Acidity			Chlorides, Mg for Each 100 Cc	pH
		Free	Com bined	Total		
Acid instilled	10	28	0	28	220	2.18
Content removed	12	0	24	24	473	5.16

* Complete combination of free acid, drop in total acidity in proportion to dilution, and increase in content of chloride

animal with a fundic pouch, in which hydrochloric acid was used, the free acid became totally combined in three and a half hours. The total acidity dropped somewhat, but only in proportion to the degree of dilution and the chloride content rose (table 6)

COMMENT

Changes in the reaction of acids instilled into pouches, although present, were not sufficient to permit conclusions to be drawn. It was

somewhat surprising not to find more definite evidence of buffer activity on the part of the gastric juice, particularly of the pyloric secretions, such as one might expect in the light of previous work. It was reasoned that inasmuch as there was some change in reaction, and more in pyloric than in fundic pouches, possibly these determinations alone were not suitable indexes of the chemical nature of the content of the pouch. Subsequent results seemed to strengthen this view.

Secretion of a neutral chloride seems to be the only explanation of the rise in chloride content. Regurgitated duodenal juices and swallowed saliva are eliminated as possible sources of chlorides by the method of procedure. Another possible cause is neutralization after secretion by the gastric mucosa as hydrochloric acid. If this were the explanation, the total acidity should be increased, a condition that was not found in any experiment. As far as present knowledge of gastric physiology is concerned, it must be assumed that secretion of a neutral chloride explains these results.

Such secretion probably has little effect on the acidity of the gastric content. There may be some reduction by dilution, but this at best is not remarkable, and it is known that the buffer capacity of the sodium chloride is negligible. It is only a corollary of the more important mechanism, that of decrease in the concentration of the hydrochloric acid secreted by the mucosa of the stomach when the gastric content becomes highly acid. The nature of the acidity is unimportant, inasmuch as sulphuric acid had the same inhibitory effect. The old idea of Pavlov and of other early investigators that hydrochloric acid is secreted at a constant concentration has been almost discarded. Foster and Lambert, Carlson, Lim, Babkin and others have since shown that variations can and do occur. Hollander and Cowgill²⁴ recently concluded that the concentration of the secretion of hydrochloric acid is constant. They found a constant upper level of acidity which they believed was determined by the osmotic pressure of the blood serum. The second series of experiments strengthens the view that variations occur, as in the actively secreting pouch the secretion of hydrochloric acid was either considerably or entirely suppressed, and the secretion of a neutral chloride took place. Although a rise in total acidity was not found, this does not definitely establish that the low level of secretion of hydrochloric acid is zero. It was Lim's belief that the low level is 0.29 per cent. Also it is difficult to determine whether any definite ratio exists between the neutral and the acid chlorides secreted. If the total secretion of chloride is assumed to be constant, there may be a

²⁴ Hollander, Franklin and Cowgill, G. R. Studies in Gastric Secretion. I. Gastric Juice of Constant Acidity, *J. Biol. Chem.* **91** 152 (April) 1931.

definite ratio, but although many of the recent workers believe this to be true, the fact has not as yet been established

The drop in free acidity with the concurrent rise in combined acidity must be explained, in the light of present knowledge, as the result of combination of acid with mucin, as was Foster's²⁵ contention. Recent work by Fogelson²⁶ showed that 1 Gm of mucin will combine with from 12 to 15 cc of tenth-normal hydrochloric acid, and mucin was the only known substance present in these pouches that could combine with free acid in the experimental procedure used. The part it plays becomes more important when the rate of secretion is low, as the constant basal secretion combines with a greater proportion of the total secretion at such a time. The so-called "alkaline pyloric juice" is practically entirely mucus, as shown by Ivy and Oyama²⁷ and by Lim and Dott²⁸.

The extragastric factors that play a part in this regulation must be considered. Few, if any, physiologic mechanisms are influenced or regulated by only one factor, and the regulation of gastric acidity is undoubtedly no exception to the general rule. Indeed, it is fortunate that several factors are involved. That regurgitation of alkaline duodenal juices does occur cannot be doubted, and that some neutralization takes place following this is axiomatic. It should be considered an associated phenomenon and not the only or most important factor, as its advocates would make it, for it is known that regulation is adequate without it. It is impossible even to guess at the relative significance of the extragastric and intragastric mechanisms at any particular time. When there is a large gush of alkaline fluids through the pylorus, this may become momentarily more significant, when regurgitation does not take place, the intragastric mechanisms are more significant.

Swallowed saliva may reduce acidity, although it may play only a minor part. It is estimated²⁹ that 1,500 cc of saliva is swallowed daily. By virtue of its volume alone, its mucin content and its buffer salts,³⁰ it is conceivable that the swallowed saliva might be a minor

25 Foster, N B. The Chemical Affinity of Mucus for Hydrochloric Acid, *Am J M Sc* **133** 303 (Feb) 1907

26 Fogelson, S J. The Treatment of Peptic Ulcer with Gastric Mucin. Preliminary Report, *J A M A* **96** 673 (Feb 28) 1931

27 Ivy, A C, and Oyama, Yutaka. Studies on the Secretion of the Pars Pylorica Gastrici, *Am J Physiol* **57** 51 (Aug) 1921

28 Lim, R K S, and Dott, N M. Observations on the Isolated Pyloric Segment and Its Secretion, *Quart J Exper Physiol* **13** 159, 1922

29 Bidder and Schmidt, quoted by Mathews, A P. *Physiological Chemistry*, ed 3, New York, William Wood & Company, 1923

30 Marshall, J A. Etiology of Dental Caries, *Physiol Rev* **4** 564 (Oct) 1924

factor McClendon³¹ has expressed the belief that saliva may completely neutralize acidity when the stomach is almost empty

Ingested food stuffs reduce acidity by absorption, by actual neutralization if they are alkaline and by dilution. If the buffer capacity of a particular food is sufficient, this may be a factor, at best relatively unimportant

SUMMARY

Acid of known reaction, titratable acidity and chloride content was instilled into isolated pyloric and fundic pouches of fasting and actively secreting dogs, and after varying intervals these factors were redetermined and changes noticed

Determinations of reaction by themselves are not an adequate index of chemical changes in the gastric content

The buffering ability of the secretions of the pyloric segment is somewhat better than that of the fundus

Evidence is produced to show that intragastric regulation of acidity is probably brought about by three factors (1) reduction of the concentration of secreted hydrochloric acid when intragastric acidity has reached a certain level, and, as its corollary (2) secretion of neutral chloride by the stomach, which plays a rather minor part by dilution, and (3) a combination of gastric mucin or an unknown substance with free acid

³¹ McClendon, J. F. Acidity Curves in the Stomachs and Duodenums of Infants, Plotted with the Aid of Improved Methods of Measuring Hydrogen Ion Concentration, *Am J Physiol* **38** 191 (Aug) 1915

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS

V ACID-BASE AND ELECTROLYTE EQUILIBRIUM

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AND

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It has already been pointed out that in the last stages of fatal yellow fever in *Macacus rhesus* the urinary excretion of organic acid and phosphates is considerably increased¹ In the present paper are reported the results of more extensive studies of the acid-base and electrolyte equilibrium in this disease

METHODS

The general experimental procedures outlined in the first paper of this series² have been carefully followed

The electrolytes of the serum were determined by procedures essentially the same as those described by Peters, Wakeman, Eisenman and Lee³ Blood was withdrawn and serum separated, with anaerobic precautions, by the technic of Austin and his co-workers⁴

Blood was collected without stasis from the heart, the femoral artery or the veins of the upper extremities In certain of the normal animals attempts were made to withdraw venous blood without anesthesia However, it soon became evident from the low values for carbon dioxide that this method could not be employed The reduction of

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1 Wakeman, A M, and Morrell, C A Chemistry and Metabolism in Experimental Yellow Fever in *Macacus Rhesus* Monkeys II Nitrogen Metabolism, *Arch Int Med* **46** 382 (Sept) 1930

2 Wakeman, A M, and Morrell, C A Chemistry and Metabolism in Experimental Yellow Fever in *Macacus Rhesus* Monkeys I Concentration of Nonprotein Nitrogenous Constituents in Blood, *Arch Int Med* **46** 290 (Aug) 1930

3 Peters, J P Wakeman, A M, Eisenman, A J, and Lee, C J *Clin Investigation* **6** 517, 1929

4 Austin, J H, Cullen, G E, Hastings, A B, McLean, F C, Peters, J P, and Van Slyke, D D *J Biol Chem* **54** 121, 1922

carbon dioxide was apparently due to the exercise of struggling. In one experiment, samples of blood taken at intervals showed a progressive fall in carbon dioxide as struggling continued. It therefore proved necessary to use amytal anesthesia. Bolliger and Maddox⁵ and Chambers, Deuel and Milhorat⁶ have shown that amytal does not alter the carbon dioxide absorption curve of the blood. In one experiment, blood taken under local anesthesia from the vein of a monkey that remained quiet during the procedure, was found to contain 53.8 per cent by volume of carbon dioxide. Blood withdrawn one hundred and sixty minutes later when the animal was thoroughly anesthetized with amytal contained 54.3 per cent by volume. It was therefore concluded that the effect of amytal on the carbon dioxide content of the blood was not great enough to influence experimental data significantly. In most experiments on monkeys with yellow fever, anesthesia was employed. In a few instances moribund animals, too stuporous and prostrate to offer any resistance to the procedure, were bled without the production of anesthesia or when a local anesthetic was used. It is believed that values for carbon dioxide secured under these conditions were comparable to those secured from active animals under amytal. Serum proteins appeared to be inappreciably affected by struggling and anesthesia.

Carbon dioxide of serum was determined by the method of Van Slyke and Neill,⁷ chloride, by the procedure of Van Slyke,⁸ calcium, by that of Kramer and Tisdall,⁹ and inorganic phosphorus, by that of Fiske and Subbarow.¹⁰ Total base was determined by a modification of Stadie and Ross' adaptation of Fiske's urine method.¹¹ For the determination of proteins 1 cc of serum was diluted to 25 cc with physiologic solution of sodium chloride, and 10 cc aliquots were subjected to a macro-Kjeldahl procedure. Albumin and globulin fractions were separated by the method of Howe¹² and analyzed in the same manner.

The base-combining power of the various acid fractions was estimated by means of the factors employed by Peters, Wakeman, Eisenman and Lee.³

5 Bolliger, A., and Maddox, K. M. *J. Australia* **1**:510, 1930.

6 Chamber, W. H., Deuel, H. J., Jr., and Milhorat, A. T. *J. Biol. Chem.* **75**: 422, 1927.

7 Van Slyke, D. D., and Neill, J. M. *J. Biol. Chem.* **59**: 523, 1924.

8 Van Slyke, D. D. *J. Biol. Chem.* **58**: 523, 1923.

9 Kramer, B., and Tisdall, F. F. *J. Biol. Chem.* **47**: 475, 1921.

10 Fiske, C. H., and Subbarow, Y. *J. Biol. Chem.* **66**: 375, 1925.

11 Stadie, W. C., and Ross, E. C. *J. Biol. Chem.* **65**: 735, 1925.

12 Howe, J. P. *J. Biol. Chem.* **49**: 93, 1921.

EXPERIMENTAL RESULTS

The only important electrolyte disturbances that seemed to be distinctly referable to yellow fever involved protein, bicarbonate, phosphate, the undetermined acid fraction and calcium. Total base showed a larger range of variation among animals with yellow fever than among normal animals, but there was no especial tendency to either reduction or increase of the bases. For the most part chloride remained unaltered during yellow fever. In two instances considerable reductions were encountered, 91.7 milliequivalents and 89.5 milliequivalents, respectively. In both of these instances bicarbonate was also greatly reduced. There is no evidence in the experiments of excessive loss of chloride by vomiting or by other extrarenal modes of excretion. It seemed probable, therefore, that the chloride reductions in these cases were comparable to those described by Peters and his associates¹³ in diabetic acidosis, chloride apparently yielding its base to aid bicarbonate in the neutralization of foreign acids.

In chart 1 the proteins of normal monkeys and of monkeys with yellow fever are compared. The abscissas in this chart represent the percentage of protein in serum. The ordinates in the two lower sections of the chart indicate the number of observations. The spread of serum protein in normal monkeys seems very great. The two determinations below 5 per cent, 4.46 and 4.39 per cent, respectively, were obtained on the same day from two small monkeys used for experiments with glycogen which have been described in an earlier paper of this series. The great discrepancy between these two observations and the others, coupled with the fact that both were determined on a single day, suggests the introduction of some analytic error. Of the four determinations in which the proteins were below 5.7 per cent, one was secured from a monkey that was recognized to be distinctly sickly and two came from random studies of monkeys taken from the normal stock cage. The term "normal" as applied to those monkeys is entirely a relative one, all that can be said with certainty is that they were not suffering from yellow fever or any obvious serious illness. Of the twenty-eight observations made, twenty-one lay between 5.7 and 7.4 per cent. It is probable that this more nearly defines the limits of variation in truly normal monkeys, although in animals selected as were those used for studies on yellow fever these limits probably must be extended down to 5 per cent.

The middle portion of the chart (II) shows the serum proteins in monkeys with yellow fever. The numerals in the squares indicate the

13 Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, C. J. Clin Investigation 2: 167, 1925.

day of the disease estimated from the time when the temperature first became significantly elevated. In four instances, indicated by interrogation marks, the day of the disease was unknown because the monkeys were taken at random from stock yellow fever animals. It is at once apparent from the chart that the serum proteins are greatly reduced during the course of yellow fever, and that the reduction has a general

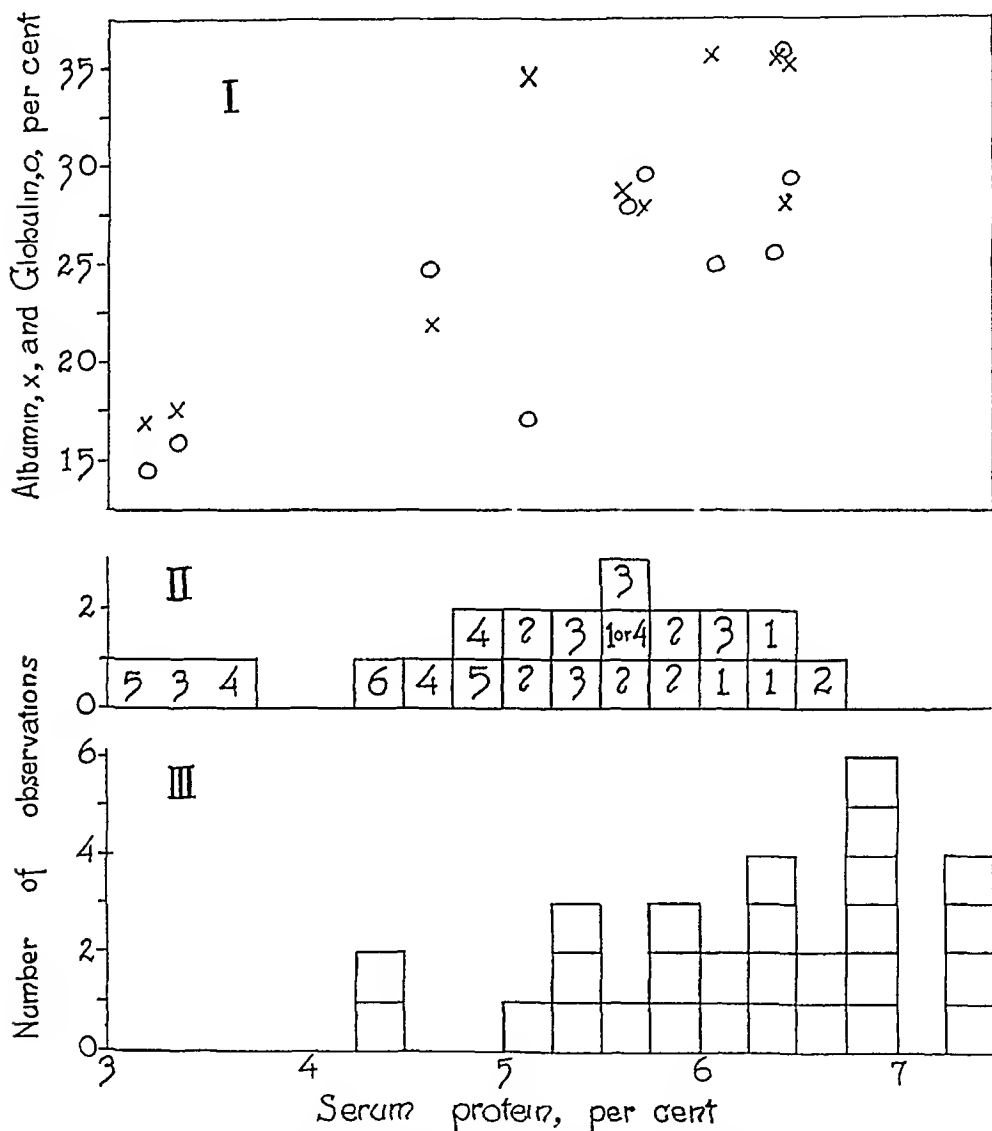


Chart 1—The serum proteins in yellow fever. The abscissas represent percentage of proteins. In *I*, the ordinates represent per cent of albumin (x) and globulin (o) in monkeys with yellow fever. In *II* and *III* the ordinates represent number of observations in monkeys with yellow fever and in normal monkeys, respectively. The numerals in the squares in *II* indicate the duration of the disease in days, calculated from the onset of fever.

tendency to increase with the duration of the disease. In general, the low figures, indicating short febrile periods, lie to the right of the chart, the high figures, longer febrile periods, to the left. There are some exceptions to this rule. This may be due to variations in the severity

of the disease, which cannot be evaluated, and the fact that the onset of fever is not a perfect criterion of the onset of the disease

In the top section of chart 1, the abscissa again represents the percentage of total proteins. The ordinate, on the other hand, represents the percentage of albumin and globulin found in those instances in which the proteins were fractionated. Observations on two normal monkeys indicate that the proportions of albumin and globulin in the serum of macacus are quite similar to those reported in human serum. It is apparent that as the proteins fall the concentration of albumin steadily diminishes. There is apparently a parallel fall in globulin. However, it becomes evident on further analysis that the globulin fraction during the first days of the disease, when the proteins are still high, has a tendency to lie above the normal level, while albumin often shows signs of diminution. One can conclude that in the early stages

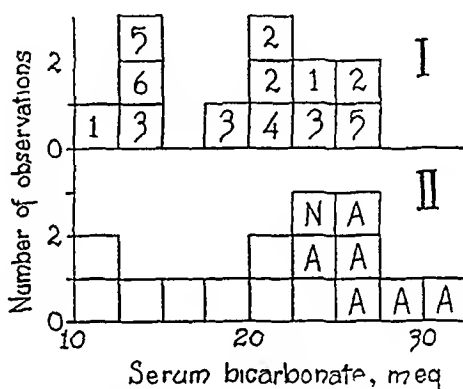


Chart 2—The serum bicarbonate in yellow fever. The abscissas represent milliequivalents of serum bicarbonate. Ordinates represent the number of observations in monkeys with yellow fever (I) and normal monkeys (II). The numerals in the squares in I indicate the duration of the disease in days, calculated from the onset of fever. The letters in the squares in II indicate that amylal (A) or local anesthesia (N) was employed.

of the disease there is an initial rise of globulin which passes off as the disease progresses, while albumin is steadily depleted from the onset to the termination.

In chart 2, the serum bicarbonate of normal monkeys (II) is compared with that of animals with yellow fever (I). In the normal series the blank squares represent animals bled without anesthetic, squares marked A, animals anesthetized with amylal, and the one square marked N, the observation noted before in which local anesthesia was employed. For reasons already discussed, it is believed that only the data secured under anesthesia can be considered as showing a normal content and can be used for comparison with the figures for yellow fever. The normal range covered by these figures coincides with the normal limits of variation found in human beings.

There is an obvious tendency for bicarbonate to decrease in the course of yellow fever. However, this fall is not quite so consistent nor so closely related to the duration and severity of the disease as is the reduction in protein.

Inorganic phosphate of serum was frequently, but not invariably increased in the terminal stages of yellow fever. In eight determinations on normal animals, values of serum phosphorus varied from 2.5 to 7 mg per hundred cubic centimeters (from 1.5 to 4 milliequivalents). In nine determinations on monkeys with yellow fever, four were above this limit, varying from 8.6 to 15.7 mg per hundred cubic centimeters (from 5 to 9.1 milliequivalents). In most instances high values for phosphate were associated with striking reductions in bicarbonate. This

TABLE 1—*Total Serum Electrolyte Balance in Monkeys with Yellow Fever*

No	Day of Fever	Protein, Milli-equiva-lents	Bicar-bonate, Milli-equiva-lents	Chlorides, Milli-equiva-lents	Inorganic Phos-phate, Milli-equiva-lents	Base, Milli-equiva-lents	Deter-mined Acids, Milli-equiva-lents	Unde-termined Acids, Milli-equiva-lents	Comment
1	3	8.1	14.3	91.7	5.0	152.0	119.1	32.9	Just after death
2	6	10.7	14.2	108.2	2.9	164.0	136.0	28.0	Moribund
3	2	15.8	22.4	113.0	*	177.0	(153.5)	(23.5)	First day of fever
4	3	12.9	18.8	112.0	*	153.6	(146.0)	(12.6)	Still active
5	1	15.6	11.4	124.5	9.1	180.5	160.6	19.9	Prostrated
6	4	8.7	21.0	110.0	1.9	163.5	141.6	21.9	Prostrated
7	3	13.1	24.7	109.6	3.4	159.5	150.8	8.7	Still lively
8	1	15.5	24.9	109.6	5.3	163.5	145.3	18.2	Still lively
9	5	7.8	14.5	89.5	5.7	149.0	117.5	31.5	Prostrated

* In these cases inorganic phosphate was not determined. For the calculation of total and undetermined acids it is assumed that the concentration of phosphate in the serum was 2.3 milliequivalents.

is illustrated in table 1. It is, however, also evident from this table that the acidosis is not caused chiefly by accumulation of phosphate.

In presumably normal animals, calcium was extremely variable ranging from 7.6 to 10.6 mg per hundred cubic centimeters. The majority of observations lay within the limits usually accepted as normal for human beings, from 9.6 to 10.6 mg per hundred cubic centimeters. In three instances of twelve, in yellow fever, calcium values were lower than any observed in normal monkeys. The observations were made in such a random manner that it is impossible to correlate these reductions with disturbances in other factors or to establish any certain connection between them and the disease. The great majority of figures for serum calcium in yellow fever distribute themselves in much the same manner as do the figures obtained from normal subjects.

EXCRETION OF ACID METABOLITES

The excretion of chlorides, inorganic phosphorus and organic acids has been measured during control, febrile and terminal periods in

TABLE 2—*Chloride Phosphorus and Organic Acid Excretion*

Date	Diet, Mg	Chlorides in Urine, Mg	Balance, Mg	Urine		Serum Chloride, Mg NaCl × 100 Ce Serum	Urine Volume, Ce
				Organic Acid, N/10 Ce	Phos- phorus, Mg		
M Rhesus M3							
September 1	520	370	150	28	12	612	
2	520	720	—200	50	5		
3	520	710	—190	58	6		
4	520	490	30	40	13		
5	520	700	—180	60	9		
		2,990	—390	245	45		
Average	520	600	— 78	49	9		
September 6	520	276	244	55	14	631	
7	520	223	297	62	28		
8	520	308	212	50	15		
9	520	430	90	54	11		
		1,237	843	221	68		
Average	520	310	210	55	17		
September 11	520	134	386	95	25	648	
12	520	321	199		81		
13	520	170	350	52	12		
		625	935	147	118		
Average	520	203	312	73	39		
September 14	520	83	437	49	21		
15	520						
16	520	350	170	37	6	650	
		433	607	86	27		
Average	520	216	303	43	13		
M Rhesus M5							
September 18	450	364	86			600	41
19	450	393	52				51
20	450	413	37	58	2		54
21	450	474	—24	51	2		45
		1,649	151	109			
Average	450	412	38	54	2		
September 23	450	252	198			628	26
24	450	527	—77		2		49
25*	450	454	— 4	62	3		66
26*	450	416	34	59	13		49
27	450	405	45				
		2,054		121			
Average	450	411	19	60	6		
September 28*	450	276	174			644	60
29	225	42	183	111	64		53
	675	313	357				
Average	337	159	178	111	64		
M Rhesus M10							
October 27	473	1,100	—627	72	26		91
28	473	666	—193	61	23		77
29	473	500	— 28	50			81
30	473	280	193	51			
November 2	473	148	325	46	35		41
3	450	241	209	47			43
		2,935	—121	327	89		333
Average	469	492	— 21	54	30		66
November 4*	322	146	182	48	53		57
5*†	236	95	141	45			58
	558	241	323				115
Average	279	120	161	47	49		57

* Animal showed fever

† Died at 11 15 p m

monkeys infected with yellow fever. Results of three such experiments are presented in table 2.

Macacus rhesus M3 was a large healthy male fed on diet no. 1.² It was inoculated on September 1 and again on September 10. The animal had a fever on September 5 and 11, but recovered and was subsequently immune to yellow fever.

Macacus rhesus M5 was a large, healthy female fed on diet no. 2. Inoculated on September 22, it showed fever on September 25, 26 and 28, and died on September 30.

Macacus rhesus M10 was a small, unhealthy female fed on diet no. 3. It was inoculated on November 2 and died on November 5 after one day of fever.

In the three examples presented for consideration two animals died of yellow fever and one recovered from the disease.

The excretion of chloride in the urine of M3 during the first control period was greater by 80 mg. per day than the intake of chloride, therefore the balance was negative. During the three remaining periods, however, there was a positive balance with no significant variation between normal and febrile periods. Organic acid and phosphorus were excreted in much larger quantities in the febrile than in the normal periods.

Essentially the same results were obtained in the two fatal cases, namely, an increase in the output of organic acid and phosphorus during the disease, with relatively no variation in the chloride in the urine.

COMMENT

These experiments seem to have established the fact that in yellow fever the serum proteins tend to fall steadily, chiefly at the expense of albumin, after an initial rise of globulin. Determinations of fibrinogen, which will be reported later, reveal striking increases in this protein fraction. It is not unlikely that the early increases in globulin and fibrinogen are merely responses to an inflammatory process. Similar increases have been reported in most inflammatory or infectious processes.¹⁴ The pathogenesis of the deficit in albumin is less clear. Urinalyses on a large number of monkeys revealed relatively slight albuminuria. Therefore, it seems unlikely that loss of albumin through the kidneys can play an important rôle. Although it has been shown that nitrogen destruction is greatly increased in the course of the disease,¹ the duration of yellow fever is so brief that malnutrition of a

¹⁴ Bruckman, F. S., D'Esopo, L. M., and Peters, J. P. *J. Clin. Investigation* 8: 577, 1930. Rowe, A. H. The Albumin and Globulin Content of Human Blood Serum in Health, Syphilis, Pneumonia and Certain Other Infections, *Arch. Int. Med.* 18: 455 (Oct.) 1916.

sufficient degree to affect serum albumin greatly is somewhat unlikely. In pneumonia in human beings, in spite of extreme toxic destruction of protein, serum albumin is usually only slightly reduced¹⁵

From table 1 it is possible to evaluate the various factors that may be responsible for the deficit of bicarbonate in yellow fever. The lack of correlation between bicarbonate and either base or chloride has already been mentioned. Although in many instances phosphate plays a significant rôle in the production of the acidosis, it is not usually the most important factor and may remain normal even when bicarbonate

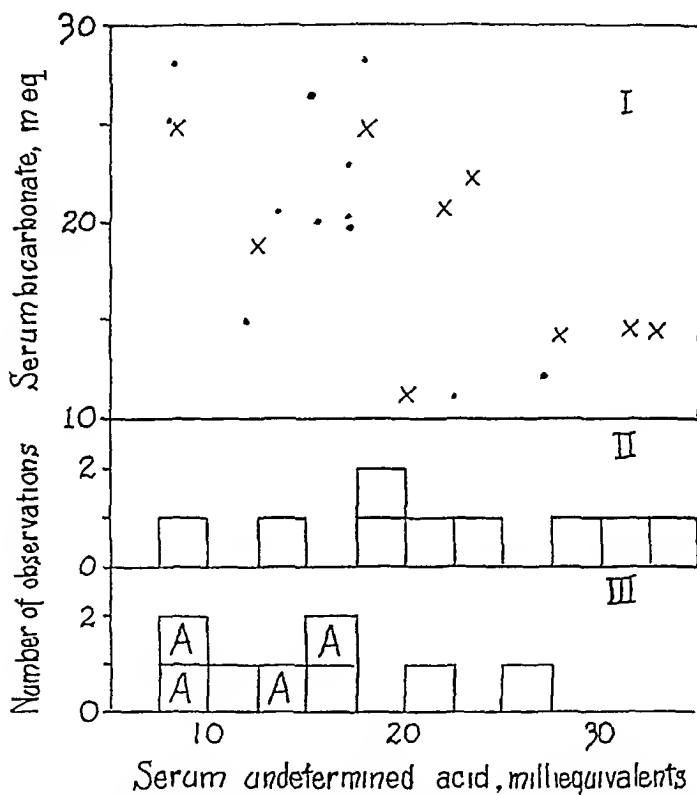


Chart 3—The undetermined acid of serum in yellow fever. The abscissas represent milliequivalents of undetermined acid in serum. In *I* the ordinates represent milliequivalents of bicarbonate in normal monkeys (indicated by dots) and in monkeys with yellow fever (\times), respectively. In *II* and *III* ordinates represent the number of observations in monkeys with yellow fever (*II*) and in normal monkeys (*III*), respectively. The letters *A* in the squares in *III* indicate that amytal anesthesia was employed.

is greatly reduced. The one element of the acid-base balance which is consistently related to the deficit in bicarbonate is the undetermined acid fraction. In chart 3, which is composed like chart 2, *II* and *III* represent the concentrations of undetermined acid in monkeys with

¹⁵ Sunderman, F. W., Austin, J. H., and Camac, J. G. *J. Clin. Investigation* 3: 37, 1926.

yellow fever and in normal monkeys, respectively. Among the normal animals only those marked *A*, i. e. the anesthetized animals, can properly be compared with the animals having yellow fever. In the latter there is a tendency for the undetermined acid fraction to increase as the disease progresses. In section I of the chart the increase of undetermined acids is seen to be inversely related to the bicarbonate deficiency. In this chart the dots represent comparisons made in normal monkeys, the crosses, those made in animals with yellow fever. High values for undetermined acids and low values for bicarbonate among the normal animals were found in those that were unanesthetized. The undetermined acid is presumably lactic acid, a product of exercise. The general trend of the relation between undetermined acid and bicarbonate in animals with yellow fever is much like the similar relation in normal animals.

From the fact, already demonstrated,¹ that urinary organic acid increases in yellow fever, it is natural to infer that the undetermined acids that accumulate in the serum are organic.

Hypophosphatemia is probably likewise connected with the increased urinary phosphate excretion.¹ The inorganic phosphate is presumably derived from the destruction of organic phosphorus compounds. In the terminal stages of the disease a diminished volume of urine or anuria may exaggerate the effects of tissue destruction.

SUMMARY AND CONCLUSIONS

The concentration of proteins in the serum of monkeys diminishes during the course of yellow fever. The reduction is chiefly at the expense of the albumin fraction. In the early stages of the disease globulin rises.

In the terminal stages of the disease serum bicarbonate is usually reduced, often to a considerable extent. The reduction is due chiefly to accumulation of undetermined acids, probably organic and, to a lesser extent, of inorganic phosphate.

No characteristic alterations were found in the concentrations of base and chloride in the serum or in the urinary excretion of chloride.

PROTEOLYTIC LEUKOCYTIC ENZYME IN LEUKEMIA

A STUDY MADE BY A QUANTITATIVE METHOD

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ST LOUIS

Since the demonstration of a rather high degree of proteolytic enzyme activity in the granular polymorphonuclear leukocytes, the presence of such leukoprotease in these and other cells of the blood has been studied in various conditions,¹ as, for example, the presence of ferments in the abnormal granular and nongranular cells present in the blood in leukemia. No studies have been reported since the development of modern microchemical methods. In this paper the results of the study of proteolytic ferment by a method applicable to small amounts of blood are described.

One point of interest in the proteolytic enzyme in the abnormal cells of leukemic blood concerns the possible relation of these cells to normal lymphocytes or to the myeloblasts of the bone marrow. Small amounts of proteolytic enzymes have been described in almost all cells, and normal lymphocytes possess little more than other types of cells, while the granular polymorphonuclear leukocytes and myelocytes have a very high degree of proteolytic activity. The presence of a relatively large amount of protease in the cells in acute leukemia, therefore, would give support to the belief that the nongranular mononuclear cells present are closely allied to the marrow elements and should be considered myeloblasts or "premyeloblasts" rather than lymphocytes. Certain authors (e g, Longcope and Donhauser² and Longcope and Cooke³) have concluded that in certain cases of acute lymphatic leukemia the cells possess proteolytic activity of a character very similar to that of the granular myelocytes and should be considered as forerunners of these cells. Other observers have not found such proteolytic activity in the

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1 Detailed reference to much of the earlier work may be found in the monograph by Noel Fiessinger, "Les ferments des leucocytes," Paris, Masson & Cie, 1923

2 Longcope, W T, and Donhauser, J L. A Study of the Proteolytic Ferments of the Large Lymphocytes in a Case of Acute Leukemia, *J Exper Med* **10** 617, 1908

3 Longcope, W T, and Cooke, J V. A Preliminary Note upon the Enzymes and the Leukocytes in Acute Leukemia, *Proc Path Soc, Philadelphia* **14** 104, 1911

cells in acute leukemia, and Fiessinger¹ stated that of twenty-two such cases reported in the literature only one-half have shown proteolytic ferment

The ideal type of blood for the estimation of leukocytic protease activity is one in which a single variety of leukocytes greatly predominates. When polymorphonuclear leukocytes are present in any considerable number, their proteolytic activity may be confusing in the interpretation of the results. In many instances the abnormal cells present in acute leukemic blood form from 80 to 90 per cent of the cells present. Any proteolytic activity present in such blood can be more readily referred to a single type of cell.

The methods used in previous studies have been similar. Blood was collected either during life or immediately after death, citrated and centrifugated. The buffy layer of leukocytes above the red corpuscles was removed by a pipet and washed with physiologic solution of sodium chloride to remove serum and its antiferment, and the leukocytes were suspended in salt solution. Protease was determined by placing a certain amount, usually 1 cc, of this leukocyte suspension in a measured quantity of coagulable protein, (e g, heated serum water) in neutral or slightly alkaline reaction and incubating for five days at 37 C, toluene being added to prevent bacterial proteolysis. At the end of the period estimations of nonprotein nitrogen were made by the Kjeldahl method on the filtrate after removal of the undigested coagulable protein by boiling with acetic acid and magnesium sulphate buffer. The amount of protease present was estimated by obtaining the difference in nonprotein nitrogen found in the tests and that present in the unincubated controls or in controls to which were added leukocytes heated to destroy their ferment. Some observers determined the amount of digestion by titration of the amino-nitrogen by the formaldehyde method.

AUTHOR'S METHOD

The method used in this study differs from those previously employed in that the hemoglobin of the blood is used as a substrate on which the leukocytic protease may act, and that the use of microchemical methods allows determinations to be made on 10 cc of blood or less. This procedure permits the study of the same patient at different times, and, by the recording of the results in milligrams of digested nitrogen per hundred cubic centimeters of blood, offers a means of quantitative comparison between different samples.

At approximately the same time that a total and stained differential leukocyte count is made, a sample of venous blood is placed in a test tube with a small amount of powdered sodium oxalate to prevent clotting. The total volume having been marked on the tube, the specimen is then centrifugated and the supernatant plasma removed and discarded, care being used to avoid taking away any cells. The cells are then washed three times in 0.85 per cent salt solution to get rid of the last traces of serum, and after the last washing the same solution is added to the tube until the original volume is reached. This is well shaken to distribute the leukocytes

evenly, and 3 cc samples are placed in large test tubes with a volumetric pipet. These are treated as follows: 1 Control—To this tube is added 21 cc of distilled water, 3 cc of a 10 per cent solution of sodium tungstate and 3 cc of two-thirds normal sulphuric acid. After shaking and filtering, the nonprotein nitrogen is determined on a sample of the filtrate and the milligrams of nonprotein nitrogen per hundred cubic centimeters calculated. 2 Protease activity in neutral medium. After the addition of 7 cc of water and a small quantity of toluene, the tube is incubated at 37 C for five days. Then 3 cc of a 10 per cent solution of sodium tungstate, 3 cc of two-thirds normal sulphuric acid and 14 cc of water are added and the nonprotein nitrogen determination made on the filtrate.

The procedure outlined is the well known method of Folin and Wu,⁴ and the determinations of nonprotein nitrogen are carried out by acid digestion and nesslerization, as usual. The results are all expressed as milligrams of nitrogen per hundred cubic centimeters of blood.

Samples of blood without leukocytes obtained by taking only the lowermost layers of cells after washing with salt solution by centrifugation show no evidence of proteolytic activity.

TABLE 1—*Protease Activity of the Blood of Normal Children*

Case	Age	Leuko cytes	Poly morpho nuclears	Lympho cytes	Mono cytes	Nonprotein Nitrogen, Mg per Cent by Volume	
						Control	Protease
1	6	8,200	57	40	3	12.9	120
2	19	5,800	69	25	6	8.1	125
3	6	6,000	72	22	6	9.0	116
4	15	8,600	68	28	4	12.0	105
5	4	7,800	43	45	12	18.0	170
6	5	5,100	83	14	3	13.0	170.5
7	5	7,400	84	12	4	18.0	180
8	9	8,200	70	25	5	13.2	152

In the tables and text the results obtained in blood determinations are spoken of as "protease," but it will be understood that they really represent the result of protease activity.

RESULTS

Normal Blood—The results of the determination of protease in the blood of a group of apparently normal persons are shown in table 1. There is some variation in different persons, but with leukocyte counts below 10,000 and the relative distribution of the cells within normal limits, the protease activity is such as to produce a figure of somewhat over 100 milligrams per cent of nonprotein nitrogen by volume. This small group will serve for comparison with later readings on abnormal leukemic bloods.

Chronic Myeloid Leukemia—Four adult patients with typical chronic myeloid leukemia were examined through the kindness of Dr. Lawrence Thompson. All had had the disease for at least a year,

⁴ Folin, O., and Wu, H. A System of Blood Analysis, J. Biol. Chem. **38**: 81, 1919.

all had received roentgen therapy, and all were in a period of clinical remission when the blood was tested. Only one case in a child was studied. Only brief notes of each case will be given.

CASE 1—H J S, a white man, aged 50, whose symptoms began one year previously, in August, 1929, had a total leukocyte count of 130,000, and since then had had eight weekly roentgen treatments. When seen on Feb 4, 1930, he was in good condition, physical examination gave negative results except for a palpable spleen, and the blood showed 24,200 leukocytes.

CASE 2—W P, a colored man, aged 28, whose first count seven months previously had been 434,000, at the time of examination still had a much enlarged spleen, the leukocytes had decreased to 15,100. Two months later another test was made, the count was 149,000.

CASE 3—W T, aged 50, colored, had been under observation for two years and had had 600,000 leukocytes with from 90 to 95 per cent myelocytes. At the time the first tests were made, the count was 103,400, but five weeks later, after roentgen treatment, the leukocytes had decreased to 20,000.

TABLE 2—*Protease Activity in the Blood of Patients with Chronic Myeloid Leukemia*

Case	Date	Age	Leuko- cytes	Poly- morpho nuclears	Myelo- cytes	Lympho- cytes	Mono- cytes	Nonprotein Nitrogen, Mg per Cent by Volume	
								Control	Protease
1	2/ 4/30	50	24,200	58	21	7	12	13.8	440
2	1/31/30	28	17,100	70.5	70	27.5	2	13.2	420
	3/14/30		149,000	20		5	5	32	1,650
3	2/ 7/30	50	103,400	46	47.5	3	3.5	22.5	280
	3/14/30		20,000	29	65	5	1	21	540
4	3/21/30	56	160,200	52	39	4	5	42.4	1,008
5	2/28/31	8	300,000	46	45	4	5	21	818
	3/10/31		23,000	77	11	8	4	15	215
	5/ 7/31		55,000	63.8	18.8	14.6	2.8	18.5	1,040

CASE 4—F S, a white man, aged 56, had had the disease about one year. Six months before the tests were made the total leukocyte count was 367,000, but following roentgen treatment the count diminished to 25,000. It had increased to 160,000 when the tests were made. The spleen was greatly enlarged.

CASE 5—E H, a white boy, aged 8, who had had asthenia and pallor for six months, had a greatly enlarged spleen and a leukocyte count of 300,000. A test was made at this time, another was made three weeks later, when the count had dropped to 23,000, following roentgen therapy, and a third after two months more, when the count had increased to 55,000.

The quantitative estimation of leukocytic protease on samples of blood from patients with chronic myeloid leukemia together with the blood picture at the time of the tests, is shown in table 2. In all instances, the figures obtained for protease are greatly increased as compared with those obtained from normal blood. The higher readings were usually found in patients with higher leukocyte counts, but this relation is not constant, since in case 3, the reverse is true. In one instance (case 5) the blood was first examined before treatment had

been given, when the leukocyte count was 300,000 and showed a greatly increased reading for protease (818), two weeks later, following roentgen therapy, the count had fallen to 23,000 and the protease had also decreased to 215, after two months the leukocyte count had risen only moderately (55,000), but the protease figure was 1,040. It would seem, therefore, that the amount of proteolytic ferment in the granular cells of the blood may vary somewhat.

The finding of an increase in proteolytic ferment in the blood in chronic myeloid leukemia is in accord with the reports of other workers. Since both polymorphonuclear cells and myelocytes are usually present in large numbers in this disease, it is difficult to determine the relative part played by each of these two types of cells in causing the proteolysis. However, since the protease content is high no matter which type predominates, it seems certain that both myelocytes and polymorphonuclear leukocytes contain an abundant protease in chronic myeloid leukemia.

Chronic Lymphatic Leukemia—We have examined only a single patient with chronic lymphatic leukemia, through the kindness of Dr H. L. Alexander.

A white man, aged 71, whose symptoms were of two years' duration, had a greatly enlarged spleen, dyspnea and weakness and had lost 40 pounds (18.1 Kg.). The leukocyte count was 505,000, practically all of which were small lymphocytes. Ten days after the first count and after roentgen therapy the count was 80,000, with 94.5 per cent small lymphocytes, 3.5 per cent polymorphonuclears and 2 per cent large mononuclears. At this time protease tests showed control, 138, protease, 63, as expressed in milligrams per cent by volume of nonprotein nitrogen.

In this single observation a relatively small amount of proteolytic activity was found in the blood cells in chronic lymphatic leukemia.

Acute Leukemia—Twenty tests for protease were made for twelve patients with acute leukemia. In every instance the disease was clinically typical, and in the five cases in which necropsy was permitted, the pathologic changes were characteristic of acute leukemia. The total number of leukocytes varied considerably in the different cases and even in the same patient, but in all there was a great predominance of pathologic nongranular mononuclear cells. Certain patients showed many of the "large lymphocytes," while in others only small numbers of such larger cells were seen, and the majority were "small lymphocytes." In every case vital and peroxydase stains were made on blood films. Sometimes very small numbers of the abnormal cells showed myelocytic granules, but almost all had no oxydase granules. The patients were of the group commonly designated as having "acute lymphatic leukemia." Brief mention of the striking features of each case is given.

CASE 1—E W, a white boy, 11 years old, had petechial hemorrhages in the skin, greatly enlarged liver and spleen and fever. Acute symptoms had been present for one week.

CASE 2—D S, a 9 year old white boy had hemorrhages in the skin and mouth, blood in the urine, fever, an enlarged spleen and cervical lymph nodes. The symptoms were first noted six weeks previously.

CASE 3—R C, a white boy, 3 years old, showed pallor, weakness, enlarged liver and spleen and fever. Later there were hemorrhages in the skin of the thigh and face, and at necropsy leukemic infiltration of the parenchymatous organs was found.

CASE 4—D R, a white boy, 9 years old, had had several attacks of fever, lasting a week or more. The spleen was enlarged, and on examination marked anemia, fever, petechiae and weakness were noted.

CASE 5—O McN, a white boy, 6 years old, had greatly enlarged cervical and mediastinal glands and spleen, with some cutaneous petechiae. The symptoms were almost entirely due to respiratory obstruction, and there was only slight fever. The child died a few hours after having been given roentgen therapy. Necropsy showed typical leukemic infiltration of the tissues, especially of the mediastinum.

CASE 6—W S, a 5 year old white boy, had a large mediastinal tumor, dyspnea and a slightly enlarged spleen. There was no hemorrhage or fever, and the symptoms were entirely those of respiratory obstruction.

CASE 7—A B, a colored boy, 13 years old, had complete flaccid paralysis of legs and a bladder and rectal sphincters, apparently due to leukemic tumor in, or pressing on, the spinal cord. He was not acutely ill, and except for the paralysis would not have sought medical aid.

CASE 8—In E S, a white woman, 30 years old, whose symptoms began four months before death, the spleen was greatly enlarged, and there was general glandular swelling. There was progressive weakness but no hemorrhage. The leukocytes numbered 30,000 two months before death, with 98 per cent lymphocytes. After intravenous treatment with antimony and potassium tartrate they had fallen to 8,000 when the first test was made. A second test was made two weeks later after the leukocytes had risen to 21,000. There was a moderate continued fever until a few days before death, when the temperature became subnormal. Marked asthenia characterized the last weeks of the disease. Necropsy revealed typical lesions of acute leukemia.

CASE 9—D K, a white boy, 10 years old, was acutely ill with ecchymotic and purpuric hemorrhages of the skin, enlarged cervical glands and spleen, and fever. The leukocytes numbered 200,000 on admission, but fluctuated considerably, reaching 4,800 at one time. The patient continued to be prostrated during the following month, with fever and, at times, severe abdominal pain. At necropsy a typical picture of acute leukemia was found with a ruptured appendix walled off by adhesions and an extensive terminal bronchopneumonia.

CASE 10—H V L, a 9 year old white boy, had a severe angina lasting a month, with leukocytes varying from 500 to 3,600. The diagnosis was agranulocytic angina. Following twelve transfusions the patient was discharged two months after the onset, apparently well and with a normal blood picture, except for the presence of a few myelocytes. One month after discharge he was readmitted to the hospital with well marked enlargement of the lymph nodes and spleen, some petechial hemorrhages and the blood picture of acute leukemia. Later, fever, marked prostration and toxicity were accompanied by a great decrease in blood protease.

CASE 11—M C, an 8 year old white girl, had anemia, asthenia, slight general glandular enlargement, a large spleen and fever

CASE 12—S B, a 4 year old white boy, had enlarged cervical and mediastinal glands when the first test was made. Fever, marked asthenia and enlarged spleen had developed when the second test was made two months later

The single determinations of protease (cases 1 to 7) in table 3 show a variation of from 17.5 to 360 mg in the various patients, and in one instance (case 10) the reading was 750 mg. These variations in protease were apparently not altogether dependent on the number of leukocytes, because some patients with high leukocyte counts gave low readings for protease and others with lower counts had a higher amount

TABLE 3—*Blood Picture and Protease Activity in Acute Leukemia*

Case	Age	Leuko- cytes	Nongranular Leuko- cytes, per Cent	Poly- morpho nuclears, Number	Nonprotein Nitrogen, Mg per Cent by Volume		Before Death	Temper- ature, C
					Control	Protease		
1	11	240,000	96	9,600	13	60	2 weeks	39.6
2	9	420,000	96	16,800	18.3	165	1 day	39
3	3	18,000	86	2,500	10	38.3	1 month	39
4	9	33,000	92	3,600	10	17.5	2 months	39
5	6	320,000	92	25,600	20	340	3 days	37.4
6	6	33,000	93	2,300	12	342	2 months	37.2
7	13	103,000	97	3,100	24	360	2 months	37.6
8	30	8,200	76	2,000	6	17.5	2½ weeks	38.6
		21,000	75	5,000	12.9	60	3 days	36.4
9	10	80,000	97	2,400	9.6	67	1 month	39
		18,500	90	1,800	7.8	24	3 weeks	40
		130,000	90	13,000	15	21	1 week	39
		300,000	96	12,000	9	24	Postmortem	
10	9	37,600	78	8,200	32	750	1 month	37
		115,000	98	2,300	20	115	10 days	37.8
		163,000	98	3,300	12	26.7	3 days	39.4
11	8	10,400	84	1,700	16	38	6 weeks	38.8
		15,200	95	800	11.7	27	5 weeks	39
12	3	145,000	91	13,000	15	237	2 months	37.6
		242,000	94	14,500	10	110	5 days	39

of protease. Since it was evident that some other factor influenced the amount of protease present, an analysis was made of the clinical condition of the patients at the time of the examination of the blood. In acute leukemia there are periods, often toward the end of the disease, during which the patient shows striking clinical evidence of severe systemic disturbance, such as, for example, pyrexia, hemorrhages and intoxication. There are also periods, usually earlier in the disease, in which the clinical signs may be merely moderate anemia and asthenia with enlargement of the spleen and lymph nodes, but without toxic symptoms. The presence of febrile reaction usually indicates toxicity attributable to the leukemia. The temperature at the time the tests were made has also been tabulated, and a rather striking correspondence between the presence of fever and a low reading for blood protease is seen. This is evident, not only in various patients, but also in the

same patient when readings were made at different times. In every instance the low values were found when the patient was obviously ill and toxic.

The possible influence of the granular polymorphonuclear leukocytes present in leukemic blood on the protease content must be considered. In table 3 are tabulated the estimated numbers of these cells in each specimen tested. It is difficult to draw definite conclusions as to this point, but in certain instances, notably case 9, a rather large number of granular leukocytes was present in blood that was low in protease. This indicates that the granular cells share with the nongranular leukocytes the loss of this enzyme.

The three instances (cases 5, 6 and 7) in which a relatively high reading for blood protease was noted occurred in children without fever or other evidence of intoxication whose symptoms were due to mechanical disturbances produced by localized leukemic infiltration. Two of them had large mediastinal masses that caused marked respiratory embarrassment with cyanosis, while the third was paralyzed in both legs from a dorsal myelitis of leukemic origin.

Among the patients for whom several determinations for protease were made during the course of the disease, the one in case 10 (table 3) is also of considerable interest in illustrating the apparent relation of the clinical evidence of intoxication to the blood protease. When first tested, this boy was afebrile and free from toxic symptoms, although the lymph nodes and spleen were moderately enlarged. The protease was 750 mg per hundred cubic centimeters of blood, similar to the high readings noted in chronic myeloid leukemia. About ten days later, a febrile attack lasting a week occurred, and another test of the blood made when the temperature had subsided somewhat showed the protease to be only 115 mg per hundred cubic centimeters, although the total leukocyte count had increased markedly. A week later when the leukocyte count was still rising, the protease reading was only 26.7 mg per hundred cubic centimeters. At this time the patient was very toxic, with continued high fever and hemorrhages. He died three days later.

COMMENT

From the instances cited and the others shown in table 3 it would seem that the nongranular cells in acute leukemia may contain protease ferment to a degree comparable to that found in the granular myelocytes in chronic myeloid leukemia. This high protease content of the cells, however, is demonstrable only before the patient has become febrile and toxic from the disease. When the disease reaches the stage in which toxic symptoms appear, the protease of the cells is markedly decreased or almost absent, even though the total leukocyte count is very high.

In morphologic appearance the abnormal nongranular mononucleated leukocytes present in acute leukemia resemble lymphocytes or lymphoblasts found in the lymphatic tissues, and it is common to speak of the disease as acute lymphatic leukemia. However, in the acute forms of leukemia, it is significant that the elements of the blood chiefly affected are those originating in the bone marrow, since the polymorphonuclear leukocytes, the platelets and the red corpuscles are all constantly decreased. The abnormal nongranular cells that appear in the blood, by their high content of protease, seem also biologically closely related to bone marrow tissue, as the only other cells known to be characterized by such abundant protease are myelocytes and polymorphonuclear leukocytes. These facts make it much more probable that the abnormal cells in acute leukemia have their origin in the bone marrow, and that the disease should be considered primarily one affecting the hematopoietic marrow tissues rather than the lymphatic tissues.

It is true that the lymphatic glands may become enlarged in acute leukemia, although this enlargement is often relatively insignificant and tends to occur late in the disease. Microscopically, the cells found infiltrating the lymph glands are apparently identical with the abnormal nongranular mononuclear cells of the blood. If these cells originate in the lymph glands and subsequently pass into the blood they should be considered lymphocytes. However, there is no evidence that these infiltrations of the lymph nodes are not secondary, with the cells originating in the marrow and passing to the lymph nodes by way of the blood stream like similar cell infiltrations of the liver, spleen and kidneys, which are rather constant in the disease. The presence of considerable amounts of proteolytic ferment in these cells is evidence that strongly suggests that their origin is myeloid rather than lymphoid. Their relation to myeloblasts or other marrow cells and the nature of the changes that lead to the loss of protease activity during the course of the disease can only be conjectured.

Since there is some question about the justification for considering the abnormal nongranular leukocytes of the acute form of leukemia as lymphocytes, it would seem proper to designate the disease as "acute leukemia" rather than "acute lymphatic leukemia."

SUMMARY

A method for quantitative determination of protease activity applicable to small amounts of blood has been used in studying patients with leukemia. The results are expressed in milligrams of nonprotein nitrogen per hundred cubic centimeters.

In chronic myeloid leukemia the blood protease was found to be considerably increased. Although the readings usually varied in direct

relation to the leukocyte count, there were certain exceptions that indicated that the protease activity of these cells might vary under certain conditions

In the single case of chronic lymphoid leukemia studied the blood protease was decreased

In acute lymphatic leukemia, both high and low values for blood protease were found. An analysis of twenty determinations made on twelve patients indicates that the nongranular leukocytes in acute leukemia may have a rather high protease activity, comparable to that of the granular cells, but that this protease content becomes markedly decreased in the late stages of the disease. A similar decrease in protease activity of these cells accompanies toxic periods, shown by fever and prostration, which may occur in the course of the illness.

The fact that the abnormal nongranular leukocytes of acute leukemia may contain abundant protease, even though their enzyme content may be decreased in certain stages of the disease, is interpreted as evidence that these cells should be considered more closely related to the granular myelocytes than to the true lymphocytes, and that their origin is in the bone marrow and not in the lymphatic system. It seems probable that the essential site of disturbance in acute ("lymphatic") leukemia is the bone marrow and not the lymphatic system.

CHRONIC GASTRIC ULCERS

HISTOLOGIC OBSERVATIONS ON THE FACTORS UNDERLYING THE HEALING OF LESIONS PRODUCED EXPERIMENTALLY IN RABBITS

A N FERGUSON, M D

CHICAGO

In 1928, I reported cytologic observations on the regenerative phenomena that followed the surgical removal of large areas of gastric mucosa in the dog¹ These areas represented experimental acute gastric ulcers Such acute lesions healed rapidly, and the process was followed from the earliest changes to complete restoration with newly differentiated epithelium The type of cell responsible for regeneration of this epithelium was identified and was found to be the so-called foveolar cell which forms the foveolae of normal gastric glands

Similar work was attempted in the rabbit, but it was evident that, with the technic employed, the process in this animal was somewhat different from that observed in the dog The acute lesions in the rabbit instead of healing tended to become chronic ulcers in a large percentage of the experiments Reports on a few of these ulcers were included in my previous article The successful production of such chronic lesions gave an opportunity for study of the healing processes in experimental chronic gastric ulcers I have since produced another series of chronic ulcers of this kind in which the lesions varied in age from 3 months to more than 2 years, they represented all stages from ulcers with practically no healing to almost completely healed lesions A cytologic study of this series of experimental chronic gastric ulcers in rabbits constitutes the present report

MATERIAL AND METHODS

The animals used were large rabbits (mostly Flemish giants) weighing between 4 and 5 Kg An effort was made to use old rabbits, and all of them were at least adults About 60 per cent were females After their recovery from the operation to be described, some of these animals were used for breeding purposes without any apparent influence on the experiments

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1 Ferguson, A N A Cytological Study of the Regeneration of Gastric Glands Following the Experimental Removal of Large Areas of Mucosa, *Am J Anat* 42 403, 1928

As in previous experiments reported, the animals were operated on on a full stomach, and food was left in their cages so that they might eat as soon as they chose after operation. Their diet consisted uniformly of carrots, oats and hay and, frequently, lettuce. All operations were done with aseptic technic under ether anesthesia. An incision was made in the anterior wall of the stomach at about the junction of the body of the stomach with the pyloric portion. This original incision extended through the serosal and muscular coats down to the submucosa and underlying mucosa but not through these layers. One edge of the muscular coat was then lifted up, and under-cutting was performed through the submucosa for about 2 cm. A circular area of the exposed mucosa, at least 1.5 cm. in diameter, was then excised by means of scissors, after which the original incision in the muscular coat was sewed together. This left the line of suture in one side of the floor of the ulcer.

The primary mortality from these operations was rather high, death being due to perforation of the stomach at the site of the ulcer, perigastric abscess or incidental infections. Animals that survived were allowed to live for varying periods. A series of lesions (eighteen) was obtained ranging in age from 95 days to 2 years, 1 month and 17 days. The usual length of life of a normal Flemish giant rabbit is about five years. Therefore, a lesion of over two years' duration occupies a large part of the animal's life cycle.

MICROSCOPIC TECHNIC

All of the areas of ulcer were pinned on cork and fixed in a formaldehyde-Zenker solution, after which appropriate blocks were embedded in paraffin. Sections were cut serially 5 microns in thickness. The following general and differential stains were employed: (1) Ehrlich's hematoxylin and eosin, (2) Mallory's connective tissue stain, (3) iron hematoxylin and muci-carmin and (4) Bensley's tricolor stain (Klem²).

MACROSCOPIC OBSERVATIONS

When the animals were opened for removal of the experimental tissues, surprisingly few adhesions were found in the region of uncomplicated ulcers. In some cases a collection of fatty tissue, sometimes as large as an almond, was adherent to the stomach wall, but often there was no external evidence of ulcer whatever. Especially was this true of the older specimens.

Usually the site of the ulcer was recognized without difficulty, and chronic ulcers were plainly evident (fig 1, *A* and *B*). In partially healed lesions the extent of the regenerated epithelium could be grossly estimated. This varied from only a small amount of epithelium extending centrally onto the floor of the ulcer in some specimens (fig 1, *C*) to a complete covering in others (fig 2). Gradations between these extremes were collected (fig 1, *D*). Almost completely healed ulcers were recognized by the raylike arrangement of small rugae about them, by the roughened and slightly depressed surface of the regenerated epithelium of the mucosa and by their whitish appearance in contrast

² Klem, R. L. The Granule Cells of Paneth, *Am J Anat* 5: 315, 1906

to the surrounding darker mucosa. The whole had a distinctly puckered appearance. In a few cases healing was so complete that the areas of ulcer could not be recognized definitely, and such specimens were discarded as completely healed lesions unrecognizable grossly.

The mucosa just peripheral to the margin of each ulcer, especially in the more chronic ones, was thrown up into many small irregular

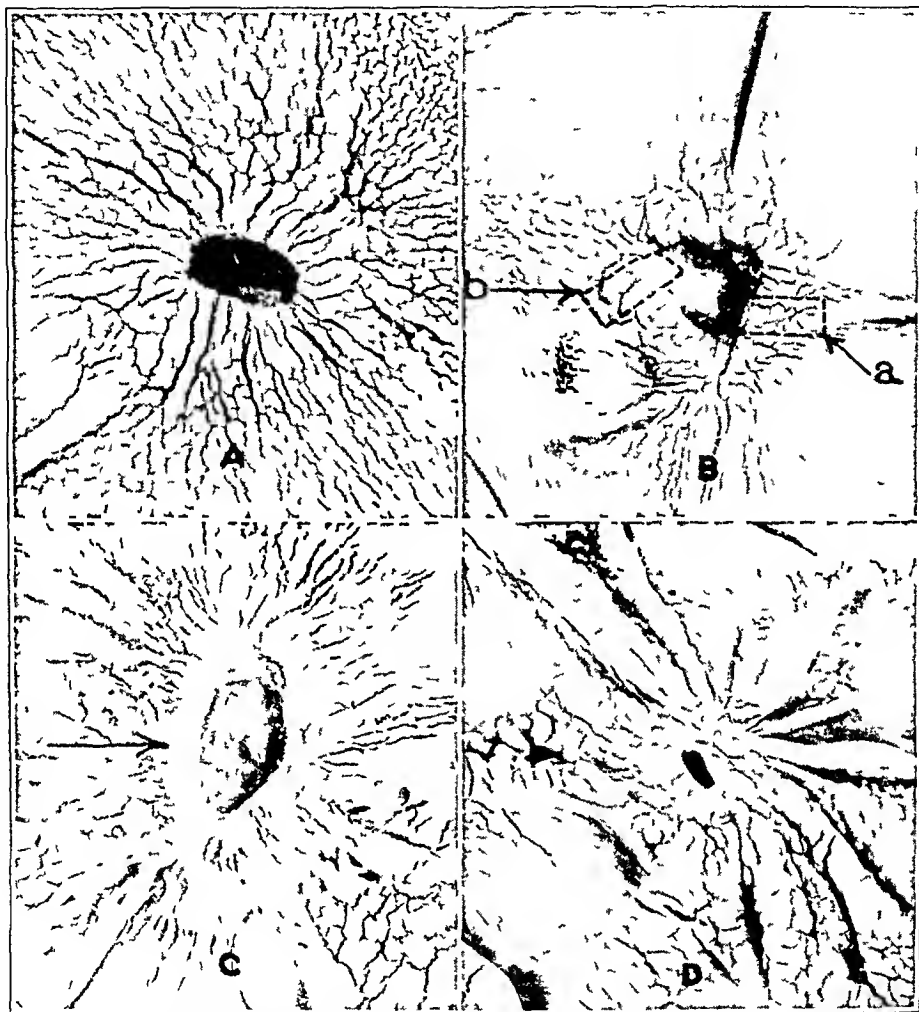


Fig 1—*A*, surface view of a chronic ulcer 3 months and 13 days old. There is no apparent healing although it is only about half the size of the original lesion made surgically. Approximately natural size. *B*, surface view of a chronic ulcer 2 years, 1 month and 17 days old. It is about one half the size of the original lesion. Approximately natural size. *C*, surface view of an ulcer 9 months and 9 days old. Regeneration of epithelium can be seen in the crescent indicated by the arrow. Approximately natural size. *D*, surface view of an ulcer 10 months and 28 days old. Considerable healing has occurred, and only a small crater remains. Approximately natural size.

elevations instead of the usual smooth membrane (fig 1, *B*). This zone, extending about 5 mm peripherally, suggested a piling up of the epithelium in this region. In several ulcers the linen suture string

placed in one side of the base at operation protruded from the crater of the ulcer (fig 2) In some specimens this extended as a loop from one side of the crater to the other

A study of the table brings out two points first, even though an ulcer tends to remain chronic (for example, 24), its size as compared to the original lesion decreases considerably Second, by itself, the age factor is relatively unimportant Some lesions tend to heal in a few months while others continue their tendency toward chronicity even after two years The essential factor determining the rate of healing is apparently, as will be seen later, the relative balance existing between the destructive and the reparative factors

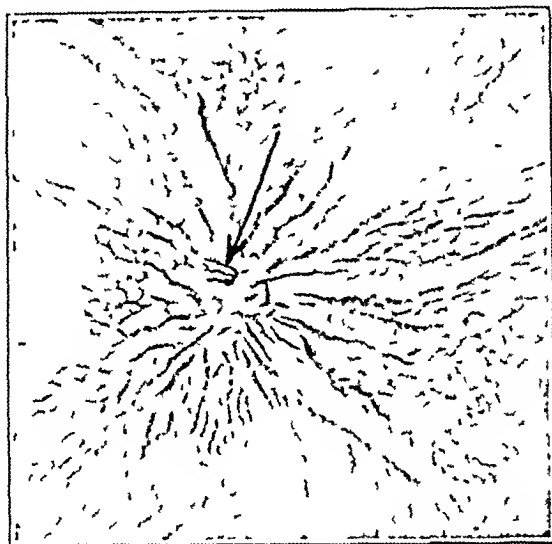


Fig 2—Surface view of an ulcer 9 months and 9 days old It is almost completely healed The suture string, indicated by an arrow, can be seen protruding Approximately natural size

Age and Size of Ulcers

Number of the Animal	Age of the Ulcer in Days	Size of the Ulcer in Millimeters
19	95	3 by 3
2	100	12 by 14
24	105	4 by 7
18	120	Edges approximated, almost healed
11	164	1 by 1
20	213	3 by 3
17	224	Edges approximated, almost healed
25	253	6 by 11
9	257	Edges approximated, almost healed
10	258	Edges approximated, almost healed
3	296	1 by 2
23	333	1.5 by 3
21	401	Edges approximated, almost healed
6	472	Edges approximated, almost healed
1	515	Edges approximated, almost healed
26	562	1 by 1
5	734	0.5 by 2
7	778	5 by 7

MICROSCOPIC OBSERVATIONS

The ulcers produced in these experiments apparently became chronic soon after they were formed, and their subsequent course depended on whether they tended toward further chronicity or toward healing. All, however, showed attempts at healing and repair. The amount of healing varied a great deal in the different specimens, some tending to remain chronic, others being partly healed and still others almost completely repaired. A description of the microscopic features of any one ulcer, would depend, therefore, on the amount of healing effected and

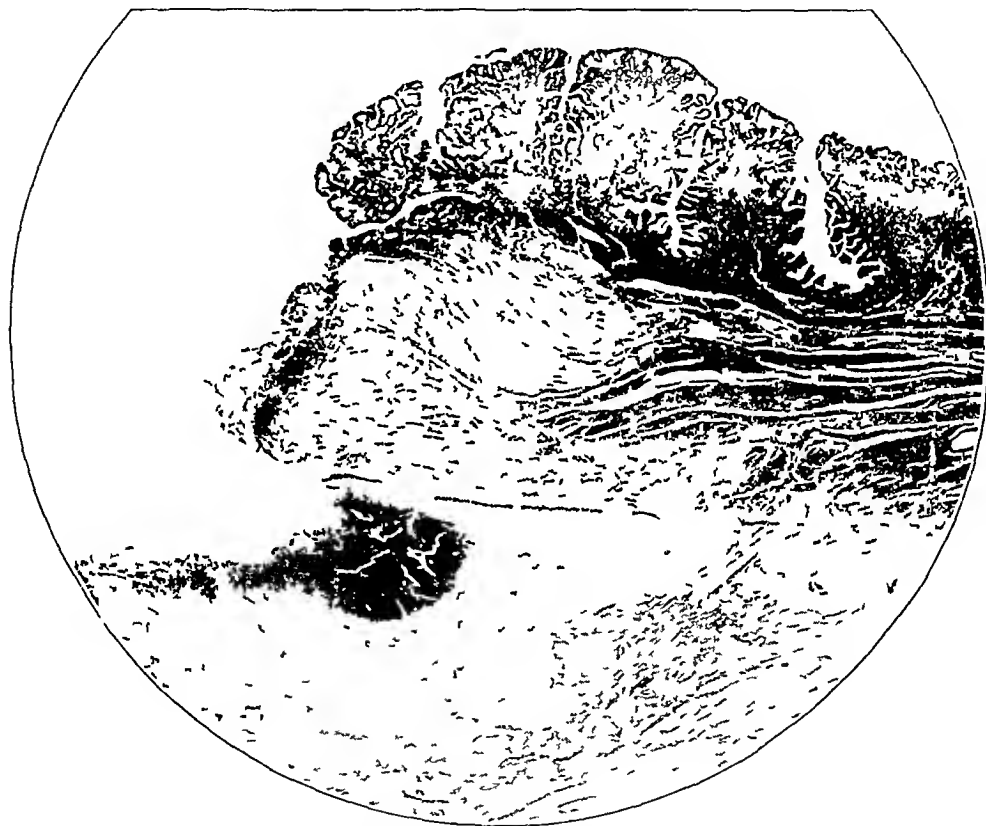


Fig. 3—A section through the cardiac side of the chronic ulcer shown in figure 1, *B* (taken from region indicated by arrow *A*), showing the epithelial folds described and the undercutting of the base at the margin. The densely stained superficial material on the floor of the crater is the necrotic layer of the base. Magnification, $\times 18$.

the character of the base, irrespective of its age. A conception of the microscopic conditions prevailing can be easiest gained by a description first of an ulcer with a tendency toward chronicity, then of a lesion almost completely healed and, finally, of intermediate stages between these extremes.

Typical Chronic Ulcer.—For the description of an ulcer with chronicity, the one obtained from rabbit 7 was selected (figs 1 *B*, 3, 4,

5 and 8) This lesion was made surgically two years, one month and seventeen days before the animal was killed and the ulcer examined. As one approached the margin of the ulcer, from areas of normal stomach tissue, all layers of the stomach were gradually increased in thickness. This condition began approximately 5 mm from the margin of the ulcer. Examination of the mucosal layer showed that it was composed of folds (fig 3) instead of the usual rather regular glandular arrangement. The largest folds bordered the crater of the ulcer and tended to lean toward it. The epithelium between these folds reached down in many places almost to the muscularis mucosae. Parietal and

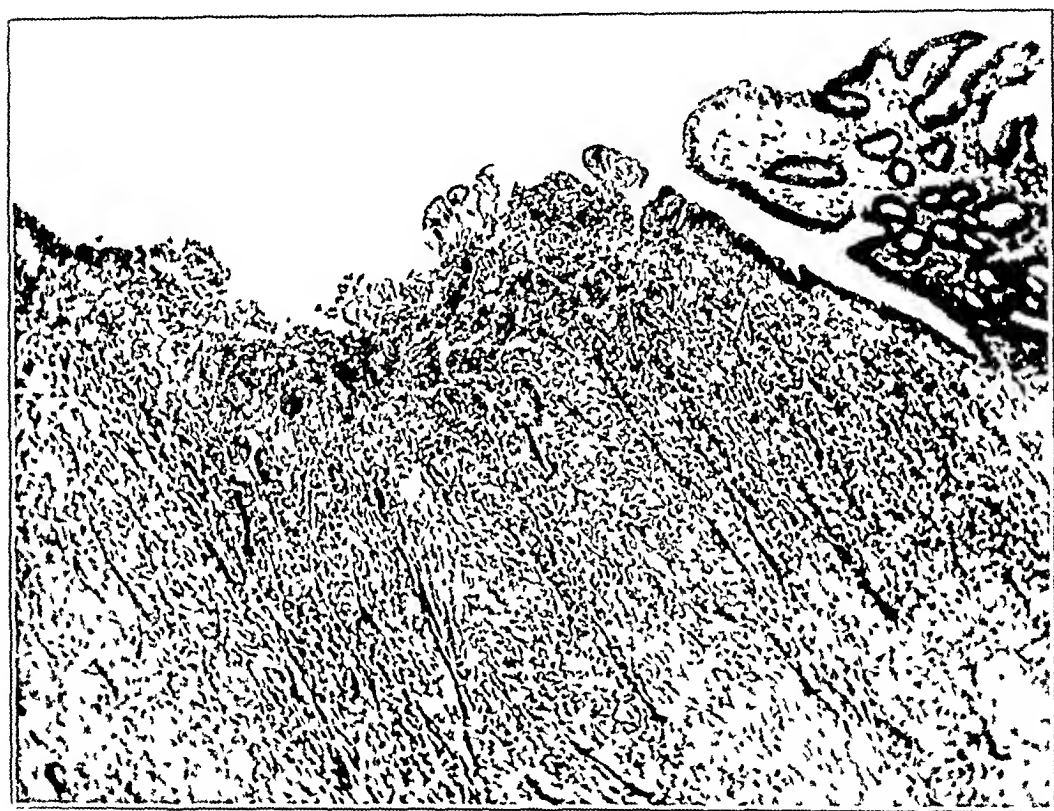


Fig 4—A section through the pyloric side of the chronic ulcer shown in figure 1, *B* (taken from region indicated by arrow *B*). The marginal epithelium extends out onto the surface for a short distance. There is very little undercutting of the margin at this location. Magnification, $\times 90$.

serous chief cells gradually disappeared as the margin was approached, so that the last folds were composed entirely of foveolar cells. Finally only a narrow rim of flattened cells extended for the distance of a few cell breadths on the surface of the ulcer (figs 4 and 5). It has previously been shown that these foveolar cells are the ones responsible for regeneration of the mucosa.¹ Connective tissue elements between the glands forming this epithelium were increased over the usual amount and there was some infiltration of leukocytes, especially eosinophils and plasma cells.

As the deeper layers of the stomach wall increased in thickness, approaching the margin of the ulcer, the submucosa was correspondingly decreased until finally it disappeared altogether. At the same time, smooth muscle fibers diminished in number in the tunica muscularis, and a compensatory amount of connective tissue appeared until, within about 1.5 mm. of the margin, the wall was composed entirely of a mass of connective tissue which continued into the base of the ulcer (fig. 3).

The base or floor of the ulcer was composed of two main layers covered externally by serosa (fig. 3). The first or superficial one may



Fig. 5—A higher magnification of part of the section shown in figure 3, showing the epithelial cells extending furthest onto the floor of the ulcer. Magnification, $\times 150$.

be called the necrotic layer. It formed the floor proper and occupied about one fifth of the thickness of the base. It was composed of cell debris and nuclei that stained darkly with hematoxylin. Many of these latter components were lobulated, and it is assumed that they had their origin in disintegrating leukocytes. This surface layer changed rather abruptly into the underlying or connective tissue layer which was composed of a mass of fibroblasts and young connective tissue cells with many blood vessels. The fibroblasts had rounded nuclei and large amounts of cytoplasm that extended into branched processes. Apparently

these cells were exhibiting great proliferative activity. The deeper part of this layer was somewhat more dense than the stratum just beneath the necrotic layer. It also contained some collagenous fibers arranged indiscriminately. Many leukocytes, especially eosinophils, were infiltrated throughout this tissue. These were most numerous just beneath the necrotic layer. Considerable undercutting into the base was present at the margin, which was accentuated by some overgrowth



Fig 6—Section from an ulcer almost healed that is completely covered by regenerated epithelium. Note the early gland anlagen indicated by arrow A. Some specialized cells (parietal and serous chief cells) are present in the region indicated by arrow B. Magnification, $\times 75$.

of marginal tissue. This undercutting occurred just centrad to the point where the last epithelial cells extended out onto the surface of the ulcer, and was more pronounced on the cardiac side of the lesion (fig 3).

Typical Ulcer Almost Healed—As previously stated it was not possible to recognize a completely healed lesion positively, therefore a description of one almost healed is given. As a basis for this description the lesion from animal 9 was selected (fig 6). This lesion was examined

nine months and eleven days after it was produced surgically. There was no appreciable thickening of the total stomach wall, but the mucosa was about two thirds of the normal thickness, while the base was slightly thicker than the usual muscular coat. The mucosa was thrown up into small folds. Most of the epithelium was composed of foveolar and mucous chief cells, but some specialized cells, parietal and chief serous, were seen. These were arranged in small irregular glands with some connective tissue separating them. Apparently regeneration of the mucosa had occurred similar to that described for the dog¹ except that the process was slower. The underlying wall of the stomach was composed of a mass of connective tissue intermingled with bundles of smooth muscle fibers. There was no regular arrangement of these tissues whatsoever, and the whole had a rather compact structure. The mucous membrane rested directly on this tissue. There was no distinct muscularis mucosae and no submucosa. All the cell types present in both the mucosa and the deeper layers of the normal stomach were therefore represented in this healed specimen, but their arrangement was modified as noted. Healing, therefore, may be practically complete. Whether or not such a healed ulcer is a vulnerable area in the stomach that may give rise to another ulcer is questionable.

Specimens Intermediate Between Chronic and Healed Lesions—

The description of any ulcer intermediate between the two described above depends on two factors. One is the amount of healing, as represented by regenerated epithelium extending out onto the surface of the ulcer, while the other concerns changes in the base. Both of these are a measure of the reparative processes, if any exist, in the ulcer. In some specimens these processes were small in amount, in others considerable healing had occurred, and in several it was almost complete. In a few cases one gets the impression that healing proceeded up to a certain point and then for some unknown reason stopped. This was especially true in the ulcer obtained from rabbit 23 (fig 7), which was ten months and twenty-eight days old. Here in the angle of the undercutting in the base, many yeast cells were seen, and they may have been the factor responsible for the apparent delay of healing in this instance.

One negative observation in these experiments is of importance. In the original report¹ a few small, isolated alveoli were recorded as being seen rather deep in the floor and base of the twenty-eight and forty day ulcers in the rabbit. These alveoli were formed by a single layer of undifferentiated cuboidal cells, and some could be traced to the regenerating epithelium at the margin. The possibility of a malignant growth developing from such alveoli was considered. In fact, the present work was begun for the purpose of testing whether an experimental carcinoma of the stomach would result. The hypothesis was that

foveolar cells (which are the least differentiated cells in the gastric mucosa), in their repeated unsuccessful attempts to repair the ulcer defect may continue to revert to a less differentiated cell type until they finally break away from cell control and become malignant. The results did not support such a hypothesis. Even though the chronic ulcers occupied a large part of the life cycle of the animal used (the rabbit), in some cases (two fifths of the total number), there was no evidence of carcinoma in any of the specimens.

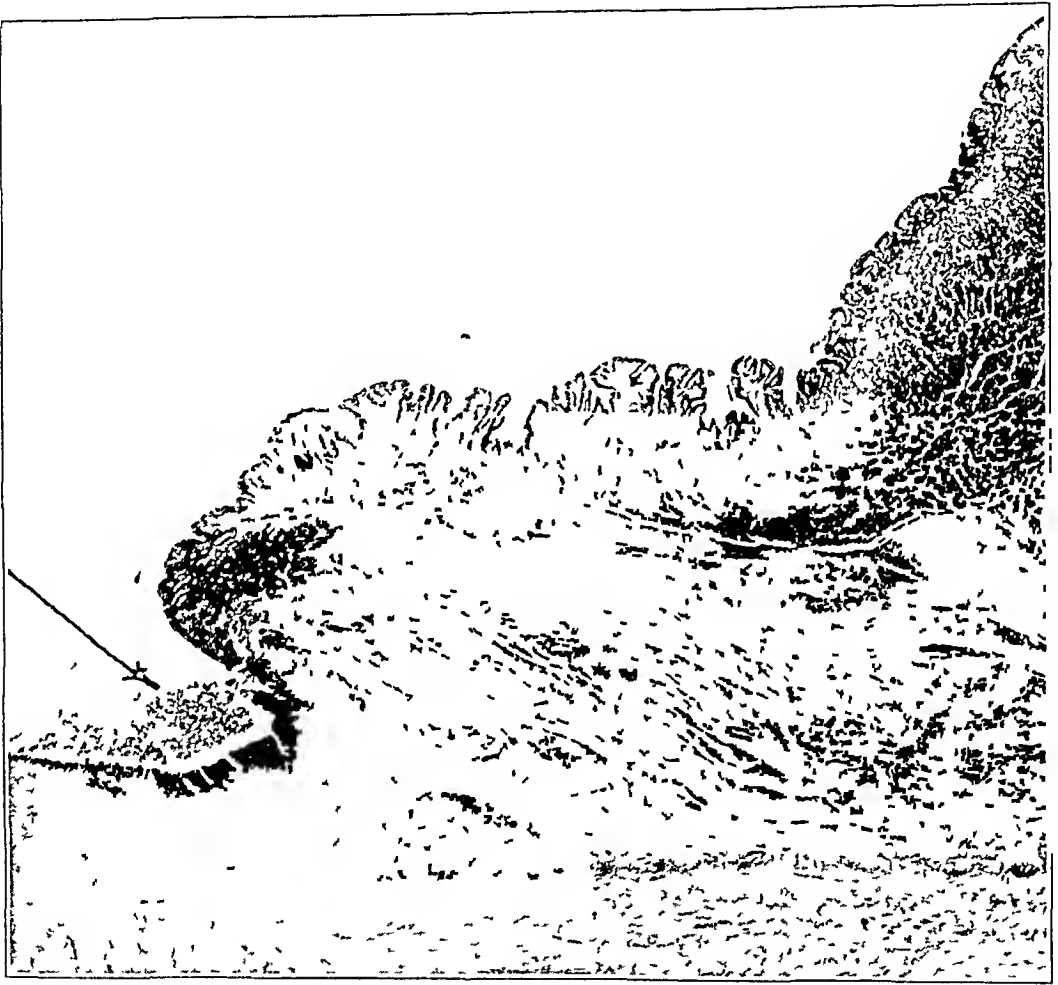


Fig 7—Section of the lesion obtained from animal 23. Considerable regeneration of the mucosa has occurred, but healing has apparently stopped. Yeast cells were present in the location indicated by the arrow. Magnification, $\times 25$.

COMMENT

A general consideration of all observations shows that there is wide variation in the healing of the experimental lesions produced in the gastric mucosa in different rabbits. In some the ulcer tends to remain chronic, while in others it tends to heal. This proved true even though the animals were fed on identical diets and kept under the same conditions. The time factor, then, is relatively unimportant in considering

any given ulcer. On the contrary, the really important features are the amount of healing, if any, or the degree of chronicity.

Another significant fact is that even though an ulcer remains chronic and without any regeneration of epithelium over its base, it nevertheless tends to decrease in size when destructive processes are not too great. This may be due to three factors. First, there is a mass proliferation of epithelium back of the margin which tends to crowd the entire margin out over the base. This is evidenced both by the many small folds seen macroscopically back of the margin and by the number of cells and mitotic figures seen microscopically. A second possibility is the loss of substance from the floor of the base. It is conceivable that, as substance is lost from the floor of the ulcer by destructive processes playing on it, there is a compensatory shrinking of the base. This interpretation is supported by the appearance of the suture string in the crater of the ulcer. Originally this string was placed just beneath the serosa at operation. Considerable loss of substance must have occurred, therefore, for this suture to appear in the crater of the ulcer. Still another possibility for this decrease in size of the ulcers is the contraction of scar tissue in the base, but this probably plays a minor rôle. Most of the connective tissue in the base of these experimental chronic ulcers is young and has very little collagen. Just how far reduction in the size of a chronic ulcer may go is problematic.

It was noted that the connective tissue in the base of these chronic ulcers was relatively young and contained many blood vessels. Apparently, destructive forces playing on the floor of the base cause such a rapid loss of substance that the underlying connective tissue does not have time to reach maturity. The large number of blood vessels indicates good vascularity and speaks against poor blood supply as the cause of chronicity. Destructive forces, to be enumerated presently, are believed to be the chief factors in chronicity.

It is evident that there are two main structures involved in the healing of a chronic ulcer, namely, the marginal epithelium and the base. The epithelium attempts to cover the base in two ways, *i. e.*, by mass proliferation, which crowds the entire margin out onto the floor of the base, and by the regeneration, from the most central marginal cells, of new epithelium that creeps out over the floor. The epithelial cells composing this margin are of a constant type. They are all foveolar cells, similar to those that form the foveolae of normal gastric glands. Thus the cells responsible for the regeneration of epithelium in acute ulcers¹ are also responsible for this regeneration in chronic ulcers. It seems that the foveolar cells stand at the margin of the ulcer waiting for an opportunity to extend out over the floor and cover it.

The work of Dragstedt and Vaughn³ supports the interpretation just advanced. These investigators sutured various organs into the wall of the stomach and exposed them to the action of gastric juice. They found that new gastric mucosal epithelium regenerated over such tissues as parenchyma of the spleen and concluded that such immature epithelial cells are quite resistant to gastric corrosion. The indications are that chronicity in ulcers is not due to a deficiency in the epithelium.

The other important structure, from the standpoint of healing, is the base. The present work supports the idea that a continual struggle occurs in the base between destructive forces (to be discussed later) on the one hand and reparative ones there is loss of substance from the floor of the base. This is evidenced not only by the necrotic layer that forms the floor and by the frequent appearance of the suture string (placed near the serosa at operation), but by the occasional occurrence of perforation. In this condition of conflict so much necrotic material and débris are present on the surface of the ulcer that it is impossible for the waiting epithelium at the margin to grow out onto the floor. If, however, reparative processes are in the ascendancy, a suitable floor is provided so that epithelium at the margin is able to gain a foothold and advance the regeneration. The extent of healing depends on the amount of these reparative processes. When they are in sufficient excess, complete healing takes place.

The destructive forces acting on the base may be mechanical (such as coarse food or foreign bodies [suture string]), chemical (such as acid and the gastric ferments) or infectious processes. Investigation of the nature and relative importance of these has been begun.

A review of the literature reveals that Crohn⁴ made a postulate that is supported by the present work. He said "It may be safely assumed that the characteristic features of an ulcer are the result of two opposing influences (1) The causative destructive factors which continued to operate and (2) The protective reaction of the organism, the reparative factors. The histologic appearance of any individual ulcer, therefore, would seem to depend on which of these two influences is in the ascendant at the time the lesion is secured." Caylor⁵ brought forth this same idea.

³ Dragstedt, L. R., and Vaughn, A. M. Gastric Ulcer Studies, Arch Surg 8 791 (May) 1924

⁴ Crohn, B. B., Weiskopf, Samuel, and Aschner, P. W. The Life Cycle of Peptic Ulcer, Arch Int Med 35 405 (April) 1925

⁵ Caylor, H. D. The Healing of Gastric Ulcer in Man, Ann Surg 83 350, 1926

Some experimentation also has been done that supports this idea of destructive versus reparative processes. Mann⁶ found that healing of ulcers occurred after diversion of the gastric contents by closure of the pylorus and a gastro-enterostomy. This prevented the gastric contents (mechanical and chemical factors) from passing over the surface of the ulcer. In the process of healing, new granulation tissue formed in the base and subsequently epithelium grew out to cover it. Fauley and Ivy,⁷ using my method of production of chronic ulcers, showed that a bland diet favors the healing process in the rabbits.

Several other observations have been made on the factors that delay or hasten healing, but most of this work has been done on acute lesions. Friedman and Hamburger⁸ found that retention of acid secretion in the stomach for an abnormal period delayed healing. Conversely, Dragstedt and Vaughn⁹ showed that the administration of alkalis aided healing. Morton⁹ showed that diversion of the duodenal contents delayed the healing of gastric lesions. He altered the gastro-intestinal tract surgically so that regurgitation of duodenal contents into the stomach could not occur. The contents were allowed to empty into the intestines several centimeters below the usual site. Hughson¹⁰ expressed the belief that a gastric ulcer near the pylorus causes reflex pylorospasm and that healing is aided by a splitting of the pylorus. Ivy¹¹ found that mechanical irritation, such as rubbing the exposed ulcer with bread crumbs, delayed healing. It is probable that some of the factors mentioned are also of importance in the healing of chronic ulcers.

SUMMARY

1. A method for the consistent production of experimental chronic gastric ulcers in rabbits is described.

2. A variation in the reparative powers of rabbits with chronic ulcers was noted. In some the ulcers tended to remain chronic while in others various degrees of healing, even resulting in complete repair, occurred.

6 Mann, F. C. Chemical and Mechanical Factors in the Experimentally Produced Peptic Ulcer, *Tr. A. Am. Physicians* **42** 224, 1927.

7 Fauley, G. B., and Ivy, A. C. Experimental Gastric Ulcer. The Effect of the Consistency of the Diet on Healing, *Arch. Int. Med.* **46** 524 (Sept.) 1930.

8 Friedman, J. C., and Hamburger, W. W. Experimental Chronic Gastric Ulcer, *J. A. M. A.* **63** 380 (Aug. 1) 1914.

9 Morton, C. B. Observations on Peptic Ulcer, *Ann. Surg.* **87** 401, 1928.

10 Hughson, W. Relation of Pylorus to Duration of Experimental Gastric Ulcer, *Arch. Surg.* **15** 66 (July) 1927.

11 Ivy, A. C. Studies on Gastric and Duodenal Ulcers, *J. A. M. A.* **75** 1540 (Dec. 4) 1920.

3 Experimental chronic ulcers in rabbits tend to decrease in size, when destructive processes are not too great, even though there is no regeneration of epithelium over the surface of the ulcer

4 Epithelium forming the margin of a chronic ulcer is composed entirely of foveolar cells. These cells constantly attempt to regenerate and repair the ulcer defect, and are successful when a floor suitable for their growth is formed. Foveolar cells are responsible for regeneration of the epithelium in both acute and chronic experimental ulcers

5 The essential factor that delays healing and produces chronicity in ulcers is that of destructive forces acting on the floor of the base. There is a constant struggle between these destructive forces and reparative processes. The outcome depends on which one is in excess and gains control

CORRELATION OF LINGUAL CHANGES WITH OTHER CLINICAL DATA

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The study of the tongue is as ancient as the practice of medicine. Hippocrates¹ has left many notes of his observations of this organ. Repeated references in his clinical descriptions of the fevers are found to the tongue that is dry or parched. Sooty and dry is another qualifying expression used by Hippocrates relative to the tongue. Again he says, "If in a winter fever, the tongue be rough, and if there be swooning, it is likely to be the remission of the fever." An even more characteristic example is to be found in the following quotation: "When there is a chronic sore on the side of the tongue the surgeon should examine whether it be not occasioned by the sharp edge of a tooth." Through the generations down to the modern period of medicine the study of the tongue has been held in high esteem not only by the medical profession, but by the laity as well. Indeed, when the clinical investigation was limited to an anamnesis, general inspection and palpation, palpation of the pulse and the examination of the physical characteristics of the dejecta, a disproportionate significance might well be placed on the observations of the tongue. Lewis² expressed a colloquialism in "Raw red tongue, raw red gut." Throughout the world alterations in the appearance of the tongue are related in the lay mind to disorders of the gastro-intestinal tract. Indeed it has frequently been considered the mirror of the stomach.

Granting the abnormalities of the tongue that attend gastro-intestinal diseases, infectious diseases, exanthems and many other diseases both local and remote, there remains a well defined group of apparent deficiency diseases which arrests the attention by reason of the similarity of their concurrent involvement of the tongue. Glossitis was reported in the severe anemias of pregnancy by Larrabee³ Isaacs,

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1 The Genuine Works of Hippocrates, translated by F Wood, New York, William Wood & Company

2 Lewis, G E. The Smooth Tongue. A Study in Deficiency Disease, Practitioner **125** 749 (Dec.) 1930

3 Larrabee, R C. The Severe Anemia of Pregnancy and the Puerperium, Am J M Sc **170** 371 (Sept.) 1925

Sturgis and Smith⁴ noted smoothing of the tongue in the anemia caused by infestation with *Dibothryocephalus latus*. Keefer and Yang⁵ determined a glossitis in patients suffering from the anemia of under-nutrition attendant on dysentery. Recovery from the dysentery and anemia was marked by coincident improvement in the glossitis. Witts⁶ described an active glossitis with denudation to actual baldness in simple achlorhydric anemia. Lewis² reported a case in which pyloroplasty was complicated by peritonitis and obstruction, and in which a jejuno-stomy was succeeded by a red tongue with low papillae. To this group may be added the more widely recognized conditions, sprue, pellagra and pernicious anemia, all of which are attended in a high percentage of instances by frank glossitis, advancing in some cases to complete baldness of the tongue. The factors common to all of these conditions, which may represent deficiencies of one type or other, are the inflammation and atrophy of the tongue.

Particular attention is directed to the association of the atrophic tongue with the pernicious and the achlorhydric forms of anemia by reason of the availability of such material for study. In the case of pernicious anemia, Hunter⁷ credited Barclay⁸ with the first description of the condition. The original text is not accessible, but Hunter's quotation⁷ rather clearly defines Barclay's patient as suffering from the anemia of pregnancy (puerperium). "Soon after her confinement she had a sore mouth, for which she applied for advice, and was ordered to leave off beer and meat, and confine herself to slops. To this she attributed her debility, as she had continued to suckle her child, and had never been able to get up her strength properly."

Likewise, in Muller's monograph⁹ at least four of the five anemic subjects reported to have suffered from stomatitis were clearly dependent on pregnancy for the inception of their trouble. His analysis of this situation is, however, worthy of preservation.

In some cases (20, 23, 29, 38, 39) there was a peculiar stomatitis. There formed in the oral cavity, especially on the tongue and on the bottom of the tongue, small ulcers of whitish color, about the size of a lentil. The same were very resistant

4 Isaacs, R., Sturgis, C. C., and Smith, M. Tapeworm Anemia, *Arch Int Med* **42** 313 (Sept.) 1928.

5 Keefer, C. S., and Yang, C. S. Anemia of Undernutrition, *Nat M J China* **15** 701 (Dec.) 1929.

6 Witts, L. J. Simple Achlorhydric Anemia, *Guy's Hosp Rep* **80** 253 (July) 1930.

7 Hunter, William. *Severest Anaemias*, New York, The Macmillan Company, 1909, vol. 1.

8 Barclay, M. *Times*, 1851, p. 480, quoted by Hunter (footnote 7).

9 Muller, H. *Die progressive perniciose Anämie*, Zurich, 1877, p. 207.

to local treatment, disappearing spontaneously or with temporary improvement of the general condition, and returning again without special cause to the great torment of the patient, since they pained greatly and rendered eating difficult, now and then almost impossible. It seems logical to assume that this stomatitis stood in relationship to the alteration of the blood, that certain chemical substances are in the blood which in greater quantity mix with the secretions of the mouth and through an irritating influence bring about the ulcers in a manner similar to that described by von Mosler for other illnesses from the parotid secretion.

Before Addison's description of the anemia that bears his name (1855), an American clinician, Dawson,¹⁰ in an exhaustive article on the tongue in diagnosis, called attention to the appearance of this structure in chlorosis. He noted that it was pallid and showed tumefactions and occasional fissures. Furthermore, it was not usually coated. "In many cases the papillae have been almost entirely obliterated, giving to the organ an unusually smooth appearance." Since methods of laboratory and clinical precision were not available at that period (1846), it is possible that Dawson actually first recognized the tongue of pernicious anemia. Further force is added to this claim for recognition by the succeeding passage, which states that a similar appearance of the tongue occurs in a nervous diathesis.

Laache¹¹ gave the most accurate description of any of the earlier writers on this point. "Die Zunge blank, Glatt, ohne Andeutung zu Papillen, dieselbe ist an den Randern gewissermassen ausgehackt, und hier hat er ein wunder Gefühl" (The tongue smooth, clean, without sign of papillae, it is to some extent hacked on the margins, and here it has a sore feeling). The relationship of the tongue to the intestinal manifestations of pernicious anemia was appreciated by Laache in a description of the mouth as skinless (*hautlos*) at the time of diarrheal manifestations. This point was further stressed by McPhedran,¹² who reported soreness of the mouth and excoriation of the anus in a patient with pernicious anemia coincident with diarrhea and a highly colored urine. Hunter¹³ recorded a case of pernicious anemia in which the soreness of the tongue "seemed to spread down into the stomach and right through him."

To Hunter¹⁴ the medical profession is indebted for the most complete study of the glossitis of pernicious anemia. He described the

10 Dawson, J. Thoughts on the Tongue as an Element in Diagnosis, *West J Med & Surg* 6 277 (Oct) 1846.

11 Laache, S. *Die Anämie*, Christiania, Malling, 1883, p. 144.

12 McPhedran, A. Pernicious Anemia. With a Report of Five Cases, *M News* 57 362 (Oct 11) 1890.

13 Hunter, William. Further Observations on Pernicious Anemia (Seven Cases). A Chronic Infective Disease, Its Relation to Infection from the Mouth and Stomach, Suggested Serum Treatment, *Lancet* 1 221, 296 and 371, 1900.

14 Hunter (footnotes 8 and 13).

injection of the margins of the tongue with the tiny vesicles that appeared in patches and shifted in location from time to time. Succeeding this inflammatory stage came denudation and atrophy of the intervening mucosa. At times these manifestations subsided with the advance of the anemia, and in other instances only after atrophy of the papillae was complete. He pointed out (1) "that the glossitic changes were of varying intensity in different cases—sometimes of an acute and subacute inflammatory character, followed later by degenerative and atrophic changes, at other times more chronic, and (2) that they are closely similar to those met with in the mucosa of the stomach, and, less commonly, of the intestine." Particularly was Hunter impressed by the distinctive mode of onset, persistence and periodicity of the glossitis. To him the tongue changes constituted the most important signpost in the study of the progress of pernicious anemia, because of their accessibility. The histologic changes described by him included the round cell exudation and proliferation in the tissues and walls of the blood vessels of the tongue. Atrophy of the epithelium succeeds necrotic and mucoid degeneration. Eventually the epithelial layer is replaced by a thin fibrous sheet, and this process of scarring dips down into the muscular tissues of the tongue, indicating the depth to which the inflammatory process has preceded. Cultural studies revealed streptococci in these deeper layers. This work was confirmed by Schneider and Carey.¹⁵

With the advent of liver therapy and the establishment of its specific virtue in the induction of blood remissions, there came a renewed interest in the glossitis of pernicious anemia. Minot and Murphy¹⁶ reported on this detail as follows:

The distressing tongue symptoms so characteristic of pernicious anemia usually vanished soon after liver was taken. Vesicles on the edges and tip of the tongue disappeared, as did the red-streaked, raw or beefy appearance. The sense of rawness or pain in the esophagus subsided. In a few patients who had a pronounced disorder of the central nervous system, the disappearance of the tongue symptoms and signs was less rapid. In none of the patients who have continued the diet well have the tongue symptoms either persisted or returned. Within a few months the tongue has usually lost its shiny appearance entirely and has appeared normal.

Ample confirmation for this conclusion is available in a vast literature, which has grown about the subject of liver therapy in pernicious

15 Schneider, J. P., and Carey, I. B. The Nature of the Glossitis in Pernicious Anemia, *Minnesota Med* **10** 214 (April) 1927.

16 Minot, G. R., and Murphy, W. P. A Diet Rich in Liver in the Treatment of Pernicious Anemia, *J. A. M. A.* **89** 759 (Sept. 3) 1927.

anemia¹⁷ Huston¹⁸ reported a uniform improvement in the condition of the mouth, "but cases having true atrophy of the tongue show no improvement in this respect" Beyond a doubt this point of view is erroneous since a number of patients with the completely bald tongue of pernicious anemia have shown a complete return to gross normality of papillary markings on liver therapy in the Wisconsin General Hospital A fairly common experience in this relation is intimated in Minot and Murphy's insistence¹⁶ that the liver therapy be adequate Starr¹⁹ reported an instance of the recurrence of glossitis in a patient who had been relieved by liver, at a later period, on the reduction and discontinuance of this therapy Isaacs, Sturgis and Smith²⁰ modified their point of view thus, "The tongue, which is frequently sore when the treatment is first begun, usually becomes normal However, the glossitis may recur in a mild way during the remission, as the ingestion of liver does not seem to be entirely specific for this symptom" Isaacs²¹ pointed out further the tendency for periodic or seasonal waves of relapsing symptoms of a mild order in patients with pernicious anemia even though the blood remission be maintained by liver therapy Among such manifestations may be a return of the glossitis

In a considerable series of patients with pernicious anemia on liver therapy in the Wisconsin General Hospital, the recurrence of the subjective complaint of rawness or soreness of the tongue with or without objective evidence of glossitis has served as a valuable clinical guide As a rule, the responsibility has been traced to some intercurrent infection or advancing central nervous involvement that might reduce the efficacy of the liver dosage Not infrequently this symptom has portended an early decline in the erythrocyte level of patients whose maintenance dosage of liver was being established An increase in the amount of liver exhibited has controlled a majority of these cases Occasionally patients on adequate liver therapy have been encountered in whom a glossitis has appeared without any other demonstrable change, subjective or objective Close inquiry into their social history has revealed some psychic or physical factor of unusual stress, the control of which has relieved the discomfort More unusual has been the

17 Starr, P Results of Liver Feeding in Pernicious Anemia, *Am J M Sc* **175** 312, 1928 Heath, E H Pernicious Anemia Treated with Liver Diet and Liver Extract, *J A M A* **91** 928 (Sept 29) 1928 Ungley, C C The Stomach and Pernicious Anemia, *Newcastle M J* **10** 14 (Oct) 1929

18 Huston, John Further Observations with the Diet Rich in Liver for the Treatment of Pernicious Anemia, *Am J M Sc* **174** 520 (Oct) 1927

19 Starr (footnote 17)

20 Isaacs, R, Sturgis, C C, and Smith, M Treatment of Pernicious Anemia, *J A M A* **91** 1687 (Dec 1) 1928

experience of Isaacs,²¹ previously related, but a few instances of this order have been met

The recent developments in the knowledge of the anemias, particularly the surpassing contributions of Castle²² to the relationship between achylia gastrica and pernicious anemia, have given a new significance to the tongue changes of this and allied conditions. The possible causal relationship between a deficiency or lack of the intrinsic factor of Castle and the glossitis of pernicious anemia and other conditions early suggested itself, however, an isolated test of Lewis² would seem to indicate that an absence of the intrinsic factor does not induce lingual atrophy. In a patient with sprue studied by him, the tongue was normal, the gastric acidity and peptic activity were normal, and the blood picture was that of pernicious anemia. The gastric juice of this patient, incubated with beef and fed to a patient with true pernicious anemia, induced no remission, whereas normal gastric juice plus beef brought about a prompt response. This clinical experience is interesting and points to a dissociation between the deficiency or other factors leading to the blood picture and the lingual atrophy of pernicious anemia.

A patient with nontropical sprue, having a normal tongue and normal gastric acidity but with the history of a complete blood remission to liver therapy, presented himself for study in the Wisconsin General Hospital. Collections of the gastric juice were made daily for a month in the hope of duplicating Lewis' observations on the intrinsic factor, but no suitable subject with pernicious anemia presented himself for study. However, it was deemed advisable to attempt a further correlation of tongue changes, especially atrophy, with common laboratory findings in the hope that certain parallelisms occurring in well recognized clinical entities might afford some clue to the basic factor

21 Isaacs, R. Systemic Relapses During Liver Induced Hemopoietic Remissions in Pernicious Anemia, *Am J M Sc* **178** 500 (Oct) 1929

22 Castle, W. B., and Locke, E. A. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *J Clin Investigation* **6** 2, 1929. Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Human Stomach Recovered After the Ingestion of Beef Muscle, *Am J M Sc* **178** 748 (Dec) 1929. Castle, W. B., and Townsend, W. C. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *ibid* **178** 764 (Dec) 1929. Castle, W. B., Townsend, W. C., and Heath, C. W. III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, *ibid* **180** 305 (Sept) 1930.

Many textbooks contain references to the relationship between the tongue and the gastric acidity. Riesman²³ noted that "in hyperchlorhydria the tongue is usually dark red, moist and clean." Wilkinson and Oliver²⁴ remarked glossitis with atrophy of the papillae among the clinical conditions associated with achlorhydria. Lewis² stated that "while a smooth tongue is most frequently seen accompanied by achlorhydria, and especially in some types of deficiency disease, the reverse does not hold."

EXPERIMENTAL DATA

Because of the apparent lack of unanimity of opinion relative to this point, the first line of attack lay in the direction of a correlation of the appearance of the tongue with the gastric acidity. When the routine aspiration failed to reveal free hydrochloric acid, an injection of histamine was given, and fractional specimens of gastric juice were withdrawn. By reason of the primary interest in the association of glossitic changes with pernicious and achlorhydric anemias, the second factor of laboratory correlation was the blood picture.

In an effort to standardize the description of the tongue, an unexpected difficulty was encountered in the proximity of terms in the literature. A sharp limitation of such descriptive terms was deemed advisable, and for working purposes the following classification has been found quite adequate.

- 1 Normal tongue
- 2 Coated tongue (furred)
- 3 Scrotal tongue (furrowed, with apparently hypertrophic ridges or plaques)
 - (a) Smooth (papillae atrophied or denuded)
 - (b) Coated
- 4 Smooth tongue (papillae atrophied or denuded)
 - (a) Complete smoothing
 - (b) Slight general smoothing
 - (c) Marginal smoothing (of lateral dorsum)

Practically all tongues may be grouped under these headings. Salivation and dryness, injection, ulceration and fissures were also recorded as separate modifications. It will be noted that no effort has been made to distinguish between actual atrophy and denudation in tongues designated as smooth.

In any study dependent on descriptive terms to meet a changing situation, there inevitably arises the pressing need for an objective method to preserve the record of conditions from time to time. Photography of the tongue is not entirely satisfactory, and many reproduc-

²³ Riesman, D. The Tongue, in Osler, William, and McCrae, Thomas. *Modern Medicine*, ed. 2, Philadelphia, Lea & Febiger, 1914, vol. 3, p. 60.

²⁴ Wilkinson, J. F., and Oliver, T. H. *Lancet* 1: 66 (Jan. 10) 1931.

tions of this nature lack the detail necessary for elucidation. The coordination of technician and subject is very difficult, hence the exposure of the tongue is frequently inadequate for descriptive purposes. Accordingly, a number of other methods were pursued with the thought of developing a technic capable of repeated application with a minimum of distortion.

The application of the ferric chloride-tannic acid method used by Elsom²⁵ to make foot prints was fruitless in the case of the tongue. The mixture of the tincture of ferric chloride, glycerin and water applied to the tongue invariably ran and blurred the print on paper, so that the subsequent addition of tannic acid in whatever form failed to give clearcut tongue prints. Citric acid solutions were next applied to the tongue, and the transfers to paper were brought out by heating. The detail of such prints was somewhat better, but not satisfactory. Various aniline dyes failed to meet the need. Of the several liquids tried, inks of the quickly drying type, as India, came closest to meeting the requirements.

Tracings on smoked paper, as utilized by Isaacs, Stungis and Smith,²⁰ were eventually adopted as affording the best results. The materials used were smoked glazed paper cut into rectangles 3 by 5 cm, thin white cards of the same dimensions, shellac diluted 1:5 in alcohol, a shallow dish and surgical gauze or absorbent cotton. The clips and frame for drying dental x-ray films proved most convenient for handling the smoked paper rectangles. In the application of this procedure the patient was fully instructed as to the purpose and plan. All dentures were removed. The tongue was blotted carefully with gauze and its position arranged by instruction as to protrusion, flattening, etc., to effect the most regular contour. Excessive salivation occasionally necessitated packing absorbent cotton pledgets beneath the tongue. The smoked paper was then applied to the protruded tongue with just sufficient pressure from the finger tips to bring uniform contact. In removing the smoked paper, the resultant negative print was then preserved by dipping into shellac and drying. The carbon or soot adhering to the tongue suggested the possibility of a second record. By dipping the thin white card into shellac and holding it in the air just short of drying before application to the tongue, a positive record may be obtained through the soot retained on the tongue. In many instances this positive print was more delicate in detail than the original or negative print. These records were then mounted on cardboard for permanent filing. Characteristic tongue prints, positive and negative, are shown in figure 1.

25 Elsom, J. E. Personal communication to the authors.

The physical nature of the tongue and its moisture offer certain handicaps not encountered in making finger prints, but with patience and careful adherence to the outlined technic, prints of the tongue may be taken that compare favorably in detailed accuracy with finger

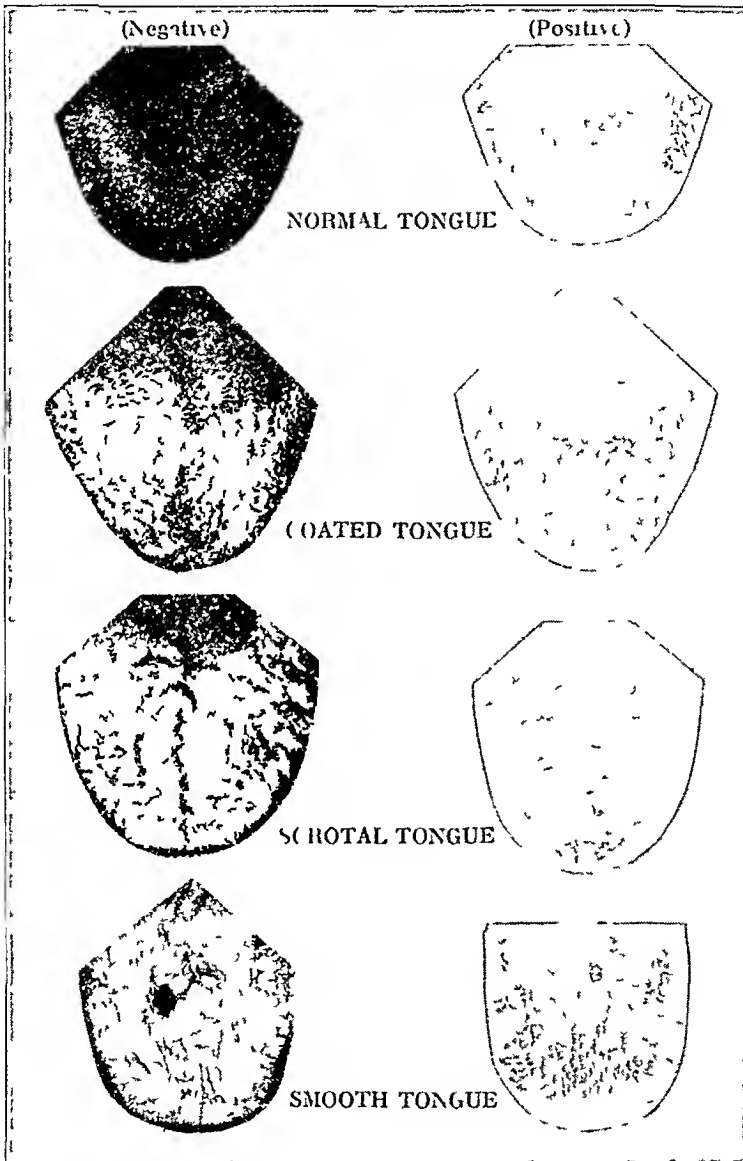


Fig 1—Tongue prints arranged for a comparison of the several types

prints (fig 2) With practice the technic proved relatively constant, and the interpretation of an isolated print usually classified the tongue as had the visual impression. The great advantage of the tongue prints lies in the fact that they constitute a permanent record, and for progress studies they should prove of inestimable value. Observations now in progress on pernicious anemia would seem to indicate that loss of the

filiform papillae is the first step toward baldness of the tongue. Later the fungiform papillae flatten and disappear. Regeneration is in the reverse order, so far as visibility is concerned.

In all, one hundred and forty subjects were included in this study. The tongue prints were taken one hundred and sixty times. Gastric aspirations after the Ewald meal were performed in all except six patients, and of the forty showing achlorhydria, fractional aspirations after histamine were made on thirty-four.

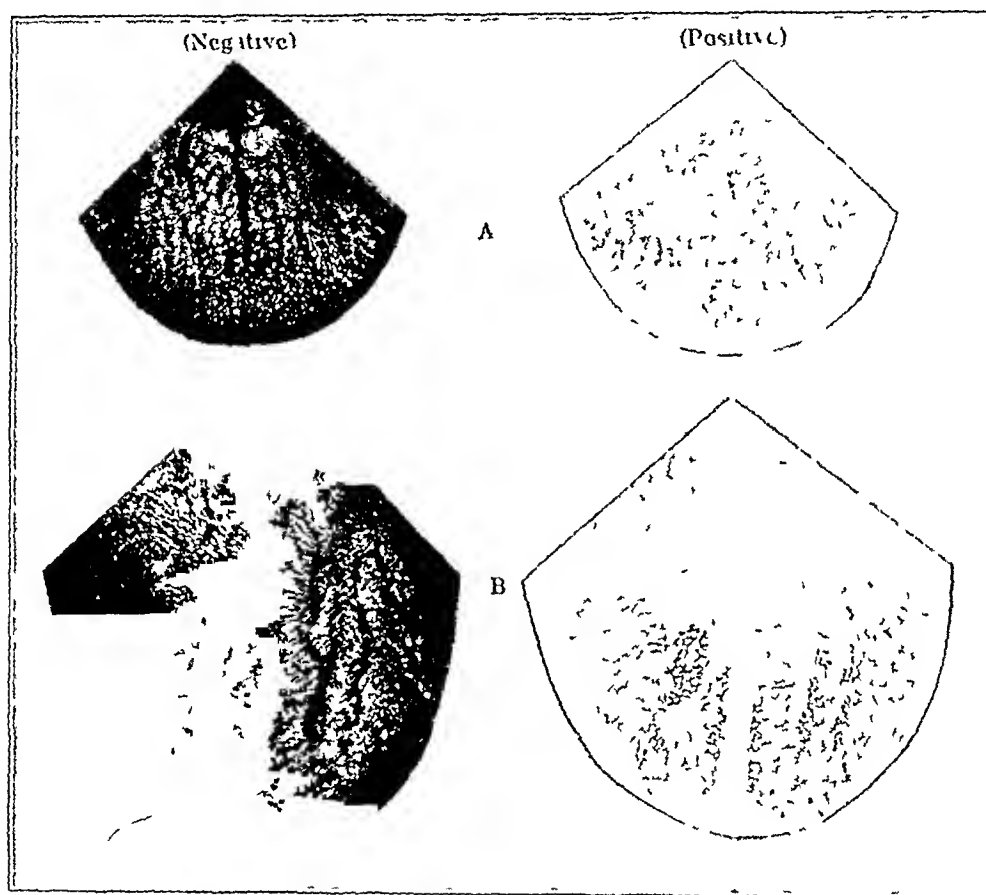


Fig 2—Tongue prints to demonstrate the accuracy of detail. *A*, detail of the tip of an atrophic scrotal tongue. *B*, a coated scrotal tongue, showing a scar to the left of the midline of the dorsum.

The succeeding tables have been extracted from the correlated data under the headings named.

THE TONGUE IN PERNICIOUS ANEMIA

The Correlation of the Type of the Tongue with Various Factors in Pernicious Anemia—There were nine cases. Seven patients had some smoothing, one complete and one slight, general smoothing, four, smooth margins, and one, a smooth scrotal tongue.

Effect of Treatment (Four patients treated, five not treated) In the four cases in which treatment was given, two tongues were normal, one had smooth margins and one was smooth scrotal. All of the five patients not treated showed some degree of smoothing (three smooth margins, one slight general smoothing and one entirely smooth)

Effect of Involvement of the Nervous System (Two cases normal, seven with combined degeneration) In both normal cases the patients had been treated, and both had marginal smoothing. Of the seven with combined sclerosis, five had some smoothing, one being scrotal as well, and two were normal.

Effect of Blood Changes (Three moderately anemic, six markedly so, none normal) In cases of moderate anemia, the tongue of two patients had smooth margins and one was of the smooth scrotal type. The six cases of marked anemia included four tongues smooth in various degrees and two normal tongues.

TABLE 1—PERNICIOUS ANEMIA

	Cases	Smoothing			Scrotal		Coated	Normal
		Com- plete	Slight General	Smooth Margins	Smooth	Coated		
Treated patients	4			1	1			2
Untreated patients	5	1	1	3				
Normal nervous system	2			2				
Combined degeneration	7	1	1	2	1			2
Moderate anemia	3			2	1			
Marked anemia	6	1	1	2				2

THE TONGUE IN GASTRIC ACIDITY

The Correlation of the Type of Tongue with the Degree of Gastric Acidity—When the gastric acidity was normal (sixty tongues), 5 per cent had slight general smoothing, 10 per cent had smooth margins, 20 per cent were scrotal, 40 per cent were coated, and 25 per cent were normal.

When there was hyperchlorhydria of any degree (30 degrees or more), there was 10.6 per cent smoothing, 23.7 per cent were scrotal, 44.7 per cent coated, and 21 per cent normal. In general, the higher the acidity, the more notable was the tendency to the scrotal type and coating of the tongue.

In cases of complete achlorhydria (thirty-nine tongues), 48.7 per cent had some degree of smoothing, and 18 per cent more were of the smooth scrotal type. Only 28.2 per cent had normal or coated tongues (7.7 per cent normal, 20.5 per cent coated). The tendency in a small series of six patients with achlorhydria not receiving histamine was not notable. In fifteen cases in which there was a small amount

of free hydrochloric acid after histamine, 46.6 per cent had some degree of smoothing, chiefly marginal, 33.3 per cent of the tongues were scrotal (13.3 per cent smooth scrotal), and 19.9 per cent were normal or coated. When these three divisions are considered together (sixty tongues), there was a general smoothing of 15 per cent, marginal of 31.6 per cent and some smoothing of 61.6 per cent (including smooth scrotal). Twenty-six per cent were scrotal, 21.6 per cent coated and only 6.6 per cent normal.

In seven cases of achlorhydric anemia, all tongues (100 per cent) were smooth in some degree (four slight general smoothing, three marginal).

TABLE 2—GASTRIC ACIDITY

	Tongues	Smoothing			Scrotal		Coated	Normal
		Com- plete	Slight General	Smooth Margins	Smooth	Coated		
Normal acidity	60		3 5%	6 10%	5 8.3%	7 11.6%	25 40%	14 25%
Hyperchlorhydria	38		2 5.3%	2 5.3%	2 5.3%	7 18.4%	17 44.7%	8 21%
Achlorhydria with histamine	39	1 2.5%	6 15.4%	12 30.8%	7 18%	2 5.1%	8 20.5%	3 7.7%
Achlorhydria without histamine	6		1	1		1	3	
Hypochlorhydria	15		1 46.6%	6 46.6%	2 13.3%	3 20%	2 13.3%	1 6.6%
Total hypochlorhydria and achlorhydria	60	1 1.6%	8 13.3%	19 31.6%	9 26%	6	13 21.6%	4 6.6%
Achlorhydric anemia	7		4 57%	3 43%				

THE BLOOD AND SEX IN GASTRIC ACIDITY

The Correlation of Gastric Acidity with the Blood Picture and Sex—Sixty per cent of the patients with achlorhydria after the administration of histamine had no anemia, 40 per cent had some degree of anemia, and 29 per cent had marked anemia. All cases with a grossly reduced gastric acidity (fifty-one) showed about the same ratio.

This figure is relatively high when compared with forty-nine cases with normal gastric acidity, of which 83.6 per cent had no anemia, and 16.3 per cent showed some degree of anemia. Only one patient (with a carcinoma) had marked anemia.

None of the fifteen patients with slight hyperchlorhydria (from 30 to 40 degrees free hydrochloric acid) had anemia. Of the eighteen patients with marked hyperchlorhydria (40 degrees or more of free hydrochloric acid), sixteen (89 per cent) had no anemia, one patient with an ulcer had marked anemia, one had slight anemia. Of a total of thirty-three cases of hyperchlorhydria, 94 per cent showed a normal blood picture.

The sex in the various acidity groups was about equally divided. Of the patients with normal acidity, 44 per cent were male and 56 per cent female. Of those with hyperchlorhydria, 42 per cent were male and 58 per cent female. Of those with achlorhydria, 56 per cent were male and 44 per cent female (including eight cases of pernicious anemia). The seven cases of achlorhydric anemia (100 per cent) were in females.

Further Analysis, Showing the Gastric Acidity and Blood Picture in Relation to the Tongue Types—Achlorhydric anemias, all of which showed some degree of smoothing of the tongue, are not analyzed in this connection.

TABLE 3—BLOOD PICTURE AND SEX IN GASTRIC ACIDITY

	Cases	Blood Picture			Sex	
		Normal Blood	Slight Anemia	Marked Anemia	Male	Female
Achlorhydria after histamine	34	20 60%	4 11 7%	10 29%	19 56%	15 44%
Achlorhydria with no histamine	6	5		1	5	1
Hypochlorhydria after histamine	11	6	4	1	3	8
Total with hypochlorhydria or achlorhydria	51	31 60%	8 15 6%	12 24 3%	27 53%	24 47%
Normal acidity	49	41 83 6%	7 14 3%	1 2%	44%	56%
Hyperchlorhydria, 30-40 degrees of free hydrochloric acid	15	15 100%				
Hyperchlorhydria, 40 degrees and upward of free hydrochloric acid	18	16 89%	1 5 5%	1 5 5%		
Total with hyperchlorhydria	33	31 94%	1 3%	1 3%	14 42%	19 57%

The Smooth Tongue—One tongue was entirely smooth, the case was achlorhydric. Of thirteen patients whose tongues showed slight general smoothing, seven had achlorhydria, one hypochlorhydria, two hyperchlorhydria and three normal acidity. Of twenty-seven patients whose tongues had smooth margins, thirteen had achlorhydria, six hypochlorhydria and two hyperchlorhydria, and six were normal.

The Scrotal Tongue—Among sixteen patients whose tongues were of the smooth scrotal type, seven had achlorhydria, two hyperchlorhydria, two hypochlorhydria and five normal acidity. Of twenty patients with tongues of the coated scrotal type, three had achlorhydria, three hypochlorhydria, seven hyperchlorhydria and seven normal acidity.

The Coated Tongue—Of the fifty-five patients with coated tongues, eleven had achlorhydria, two hypochlorhydria, seventeen hyperchlorhydria and twenty-five normal acidity.

The Normal Tongue Of twenty-six patients with normal tongues, only three had achlorhydria, one hypochlorhydria and eight hyperchlorhydria, fourteen showed normal acidity

The Blood Picture Eleven of fourteen patients with general smoothing (slight and complete) were anemic (78 per cent), thirteen of twenty-seven patients with smoothed margins were anemic (48 per cent), ten of sixteen patients with smooth scrotal tongues were anemic (62 per cent), only two of twenty patients with coated scrotal tongues were anemic (10 per cent), six of fifty-five patients with coated tongues were anemic (10.9 per cent), four of twenty-six patients with normal tongues were anemic (15 per cent)

Relation of Oral Symptoms to the Type of Tongue, Blood Picture and Gastric Acidity—Fifteen patients had the complaint of sore tongue or mouth (nontraumatic), and eleven had some degree of smoothing of the tongue (one complete, three slightly generalized, seven smooth margins) Of this group, only one had a normal tongue Eleven of the fifteen were anemic, six markedly so Nine patients had achlorhydria, two hypochlorhydria, two hyperchlorhydria and two normal acidity

Three of the patients in the foregoing group complained of dysphagia (nonneurologic) and five of dry throat, and their tendencies were about the same

The complaint of sialorrhea and the presence of salivation (six cases) had no regular relationship to the tongue picture, the gastric acidity or the blood Two tongues had smooth margins, one was coated scrotal and three were coated Two patients had slight anemia Three patients had hyperchlorhydria, two achlorhydria and one hypochlorhydria

Only one patient complained of lack of the sense of taste He had a coated tongue, hyperchlorhydria and a normal blood count None other was found who did not respond to the simplest test for the sense of taste

Eighteen tongues were noted to be injected Eleven of these were somewhat smooth (six on the margins) Three were scrotal Only one case was normal Six of the patients had achlorhydria, three others had hypochlorhydria, six had hyperchlorhydria, five markedly, only three had normal acidity Eight of the eighteen patients were somewhat anemic

THE TONGUE IN GASTRO-INTESTINAL DISEASES

The Correlation of Tongue Types and Gastric Acidity with Gastro-Intestinal Diseases—There were twenty-two cases of peptic ulcer (confirmed by the x-rays) Of this group, only one tongue had smooth margins (4.5 per cent), 23 per cent were coated scrotal, 68

per cent were coated, and one was normal. Gastric analyses on twenty of these patients showed 40 per cent to have normal acidity, 50 per cent had hyperchlorhydria, and 10 per cent had hypochlorhydria (one patient had undergone a gastro-entriostomy).

Forty-six patients (not including those with anemia) had chronic catarrhal colitis with spastic constipation (roentgen studies after a barium enema). Four tongues (8.7 per cent) showed some smoothing, mostly marginal, six (13 per cent) were scrotal (four coated), twenty-four (52.3 per cent) were coated, and twelve (26 per cent) were normal. Gastric analyses on forty-four of the patients showed 52 per cent to have normal acidity, 30 per cent had hyperchlorhydria, and 18 per cent had achlorhydria or hypochlorhydria after the administration of histamine.

TABLE 4—GASTRO-INTESTINAL DISEASES

	Cases	Smooth		Scrotal			Normal	Cases of Gastric Aspiration	Achlorhydria		Hypochlorhydria	Hyperchlorhydria	Normal Acidity
		Complete	Slight General	Smooth Margins	Smooth	Coated	Coated		With Histamine	Without Histamine			
Peptic ulcer	22	0	1 4.5%			5 22.7%	15 68%	1 4.5%	20	1 5%		1 5%	8 40%
Chronic colitis	46		1 8.7%	3	2 13%	4 13%	24 52%	12 26%	44	5 18%	1	2 30%	2 52%
Chronic cholecystitis	33		1 12%	3	1 18%	5 18%	13 40%	10 30%	32	3 32%	2	5 25%	14 43%
Carcinoma of stomach	5		1 20%	1 20%			3 60%		5	2	1	1	0 1
Neurosis	9			0	1		6	2	9	1		3 33%	5 55%

Thirty-three cases were diagnosed as chronic cholecystitis (confirmed by the x-rays after the intravenous injection of dye). Four tongues (12 per cent) showed smoothing, mostly marginal, six tongues (18 per cent) were scrotal (five coated), thirteen tongues (40 per cent) were coated, while ten tongues (30 per cent) were normal. Gastric analyses on thirty-two of the patients showed 43 per cent to have normal acidity, 25 per cent had hyperchlorhydria, and 32 per cent had a tendency to achlorhydria.

Five cases of carcinoma of the stomach were studied. Partial smoothing was noted in two and coating in three. The patients all had very low acidity, three being achlorhydric.

Nine patients were diagnosed as having a neurosis. None of them had smooth tongues, six tongues were coated, one was scrotal and two were normal. (Five of the nine patients had normal acidity, three had hyperchlorhydria and one was achlorhydric.)

MISCELLANEOUS DISEASES WITH CORRELATED DATA ON
THE TONGUE TYPE AND GASTRIC ACIDITY

Two patients with the hyperacidity syndrome had scrotal tongues

Five diabetic patients had coated scrotal tongues, all had normal or slightly increased gastric acidity. The beefy red tongue of diabetic ketosis is familiar to all, however.

Three cases of ulcerative colitis included two normal and one coated tongue. Two patients had normal acidity, one had hyperchlorhydria.

DEDUCTIONS

The observations incorporated in this report were made on an unselected group of subjects within a limited range of clinical conditions. Any deductions drawn therefrom must bear these limitations in mind. Obviously, broad generalization or attempted application to unrelated diseases would be unwarranted.

1 The series of cases of pernicious anemia is small. All of the patients not treated showed papillary atrophy of some degree. Neither the changes in the spinal cord nor the grade of anemia had any independent influence on the gross appearance of the tongue.

2 In this study patients with hyperchlorhydria rarely had smooth tongues, but often had scrotal or coated tongues. When the gastric acidity was normal, there was occasional smoothing, with a somewhat less tendency toward coating and a greater tendency toward normal tongues. When there was achlorhydria or a tendency toward it, smoothing of the tongue, or the clean scrotal type, was much more common. The corollaries to these tendencies seemed equally true.

3 In this series the patients with achlorhydria were often anemic, when the free hydrochloric acid was normal, this tendency was less pronounced, and when hyperchlorhydria was present, the occurrence of anemia was rare. When achlorhydria and anemia were combined in true achlorhydric anemia, the tongues were all somewhat smooth, the patients were all females.

4 From these observations the incidence of anemia would appear to bear a relationship to the degree of smoothing of the tongue. Normal and coated tongues were not commonly associated with anemia.

5 The subjective complaints of sore tongue and mouth, dysphagia and dry throat occurred frequently in association with the objective findings of a smooth tongue, anemia and achlorhydria. Injection of the tongue also appeared commonly with smoothing and anemia, but with either a marked hypo-acidity or a hyperacidity.

6 In organic nonmalignant disease of the gastro-intestinal tract, there was a tendency to the coated and the scrotal types of tongue.

This was more marked when hyperchlorhydria coexisted and was apparently proportional to the degree of hyperacidity. Peptic ulcer showed the most marked tendency in this direction, with chronic colitis and chronic cholecystitis following in order. Functional conditions were rarely attended by smoothing of the tongue, and had a tendency to occur in the presence of normal gastric acidity.

7 Observations on two cases of achlorhydric anemia over periods of three and four months, respectively, did not show appreciable changes in the tongue even though the hemoglobin had returned to normal. A patient with pernicious anemia inadequately treated in terms of blood response to liver therapy gave an entirely normal tongue print, demonstrating an early return of papillae to the affected member. The dissociation of the causative factors in the anemia and the glossitis of these two conditions would seem thereby to be established.

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TREATMENT OF CARDIOVASCULAR SYPHILIS

RESULTS OBTAINED IN FIFTY-THREE PATIENTS WITH AORTIC ANEURYSM AND IN ONE HUNDRED AND TWELVE WITH AORTIC REGURGITATION

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In 1930, two of us (J E M and J H D) presented before the American Heart Association a preliminary report¹ dealing with the major question of the prolongation of life as a result of treatment in 43 patients with aortic aneurysm, 90 with aortic insufficiency and 8 with various other forms of syphilitic heart disease. Because of limitations of space, it was not possible to discuss other than the one major issue, and consideration of other data was deferred. Meanwhile we have kept in touch with the patients originally reported on and have added others. In this paper, we offer a general consideration of the treatment of cardiovascular syphilis, based now on 53 patients with aortic aneurysm and 112 with aortic regurgitation. The 8 patients with syphilitic myocarditis, aortitis or angina pectoris included in the original paper have been left out of consideration, since the discussion at the meeting brought out some skepticism as to the validity of these diagnoses. We have therefore purposely limited our study to cases of aortic aneurysm and aortic regurgitation, since in these two groups of cases there can be little or no question of the accuracy of clinical diagnosis.

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From the Syphilis Division of the Johns Hopkins Hospital

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1 Moore, J E, and Dangler, J H. The Treatment of Cardiovascular Syphilis. A Study of the Duration of Life in 141 Treated and Untreated Patients with Aortic Regurgitation and Aortic Aneurysm, *Am Heart J* 6 148, 1930

We realize, and have emphasized elsewhere,² that the arrest, improvement or amelioration of symptoms of cardiovascular syphilis is *a priori* more likely if treatment is started in the stage of simple uncomplicated aortitis than if it is deferred until the advent of extensive anatomic damage to the aortic wall or valve cusps. Since there is doubt in the minds of many competent internists³ that the diagnosis of uncomplicated aortitis can be made with assurance in the absence of aneurysm or of valvular insufficiency, we have preferred to defer a consideration of the results of treatment in aortitis until we had completed a study of the accuracy of diagnosis in this condition.² The prevailing pessimism as to the beneficial effect of treatment in cardiovascular syphilis was an added reason which prompted us to review first our cases of aneurysm and aortic regurgitation. If we can show that the patients with these graver lesions can be benefited by treatment, it will be less difficult to convince others of the validity of our conclusions in uncomplicated aortitis, subsequently to appear. We realize also the limitations of treatment in cardiovascular syphilis, that the mechanical circulatory defect cannot be remedied, and that the most one can expect is arrest of progress in the inflammatory process, amelioration of symptoms and prolongation of life. It is from this point of view that we approach our material.

PROPHYLAXIS OF CARDIOVASCULAR SYPHILIS

Obviously, if early syphilis could be adequately treated in every instance, the incidence of cardiovascular syphilis would be much reduced. As has been so often said of neurosyphilis, especially tabes dorsalis and dementia paralytica, so also it may be aptly said of cardiovascular syphilis. The best way to treat it is to prevent it. Several years ago, one of us (J. E. M.) with J. E. Kemp published⁴ the details of the clinical outcome in 402 patients with early syphilis. These patients had been followed for from one to nine years after varying amounts of treatment. From time to time during the period of observation, each of them was carefully reexamined, often repeatedly, with especial emphasis on examination of the nervous system and of the cardiovascular apparatus. For purposes of study, they were divided into four treatment groups as follows:

Group 1. Patients receiving from one to eight injections of an arsphenamine product, mercury being used not at all for less than one month.

2 Moore, J. E., Dangle, J. H., and Reisinger, J. C. The Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm. A Comparison of Clinical and Necropsy Findings in One Hundred and Five Patients, *Arch Int Med* **49** 753 (May) 1932.

3 Conner, L. A., in discussion of paper by Steel, D. *Am Heart J* **6** 65, 19².

4 Moore, J. E., and Kemp, J. E. The Treatment of Early Syphilis. II. Clinical Results in 402 Patients, *Bull Johns Hopkins Hosp* **39** 16, 1926.

Group 2 Patients receiving from one to two courses of arsphenamine (from six to twelve injections), mercury having been used for at least two months during the interim between courses of arsphenamine

Group 3 Patients receiving three courses of arsphenamine (from thirteen to twenty injections) and treatment with mercury during the interim

Group 4 Patients receiving four or more courses of arsphenamine (from twenty-one to forty injections) and treatment with mercury during the interims

The results of prolonged observation, so far as cardiovascular syphilis is concerned, are summed up in table 1. These data, gathered during the study with Kemp, were unpublished at the time. In 24 patients who were inadequately treated according to modern standards, cardiovascular syphilis was observed to develop. The final diagnoses were: uncomplicated syphilitic aortitis in 21, aortic regurgitation in 2 and aortic aneurysm in 1. This type of lesion developed in 9.6 per cent of the patients in group 1, and in 5.6 per cent of those in group 2. In not a single patient among the 117 who had received three or more

TABLE 1—*Prophylaxis of Cardiovascular Syphilis by Adequate Treatment for Early Syphilis*

<i>Treatment Group</i>	<i>Number of Patients with Early Syphilis in Group</i>	<i>Number in Whom Cardiovascular Syphilis Subsequently Developed</i>	<i>Percentage in Whom Cardiovascular Syphilis Developed</i>
Group 1	196	19	9.6
Group 2	89	5	5.6
Group 3	46	0	0
Group 4	71	0	0

courses of arsphenamine and treatment with a heavy metal preparation during the interims did any evidence of cardiovascular syphilis develop during the period of observation. It was recognized that the actual incidence of cardiovascular syphilis was probably higher than we had indicated, and that in subsequent years more patients, both from the adequately and from the inadequately treated groups, would probably show this late complication. This is to be expected, since, as is already well known, and as we shall emphasize presently, the average interval of time between infection and the appearance of cardiovascular syphilis is about twenty years, while in the group of patients with early syphilis studied the maximum posttreatment period of observation did not exceed nine years. In the cases actually observed, however, the average interval between the last treatment and the detection of the cardiovascular lesion was only forty-six months, indicating that inadequate early treatment may hasten the onset of cardiac complications.

We believe that, even if the relatively short duration of observation is considered, these data are convincing evidence of the protective effect of reasonably adequate treatment for early syphilis, and that they indi-

cate that cardiovascular syphilis might be largely eliminated if it were possible to treat adequately every patient with primary or secondary syphilis. This problem will be approached from a somewhat different angle when we come to consider the question of the treatment for early syphilis received by the 165 patients with cardiovascular syphilis in this study.

INCIDENCE OF SYPHILIS OF HEART AND AORTA

Several years ago a committee of the American Heart Association, composed of Drs. Paidee, Carter, Eggleston, Krumbhaar, Marvin, White and Wilson, suggested an outline for the study of cardiovascular syphilis, including six major topics. These were incidence, pathology, symptoms, physical signs, criteria for diagnosis and treatment. The material at our disposal permits us to consider in some detail the questions of incidence and treatment. The pathology of cardiovascular syphilis has been studied in this country especially by the Cleveland⁵ and Ann Arbor groups⁶. The symptoms, physical signs and criteria of diagnosis have been reviewed exhaustively by many observers, prominent among whom is Reid⁷. These are again being critically examined by Carter and Baker of this university, who have published a preliminary paper⁸ and whose detailed studies are expected to appear in monographic form. In this paper, we purposely omit an analysis of symptoms, physical signs, roentgenologic diagnoses and electrocardiographic changes. Data on these features would obscure our main argument concerning treatment. In the patients included in this series, the diagnosis of aneurysm or of aortic regurgitation was obvious. It is important, however, to consider questions of incidence in some detail, since they help in defining our material. Furthermore, since the population of Baltimore includes a large number of Negroes, we have an exceptional opportunity not only to observe large numbers of patients with cardiovascular syphilis, but also to compare the behavior of the disease in the white and colored races.

Questions as to the incidence of cardiovascular syphilis may be approached in a variety of ways. Actuarial estimates indicate that 2 per cent of the population of the United States are suffering from

5 Saphir, O, and Scott, R. W. Observations on 107 Cases of Aortic Insufficiency with Special Reference to the Aortic Valve Area, the Myocardium, and Branches of the Aorta, *Am Heart J* 6 56, 1930.

6 Warthin, A. S. The Distribution of Latent Syphilis in the Population, De Lamar Lectures, Johns Hopkins School of Hygiene and Public Health, Baltimore, Williams & Wilkins Company, 1930.

7 Reid, W. D. The Diagnosis of Cardiovascular Syphilis. Analysis of Clinical and Post-Mortem Findings, *Am Heart J* 6 91, 1930.

8 Carter, E. P., and Baker, B. M., Jr. Certain Aspects of Syphilitic Cardiac Disease, *Bull Johns Hopkins Hosp* 48 315, 1931.

organic heart disease.⁹ White¹⁰ presented a table compiled from various sources, which points out that in different parts of the world, and in various social classes, from 5 to 25 per cent of all cases of organic heart disease are due to syphilis. Perhaps a satisfactory median would be from 10 to 15 per cent. If these estimates are correct, and if the lowest estimate (10 per cent) for the ratio of syphilitic to organic heart disease is used, there are at least 240,000 patients in this country with syphilitic heart disease.

The clinical incidence of cardiovascular syphilis among syphilitic patients in our own clinic is shown in table 2. These data are taken from Turner's paper,¹¹ and are based on the admission diagnoses of 10,000 consecutive patients with syphilis. In estimating percentages, however, only the 6,420 patients with late syphilis are used, since in the early stages of the disease detectable lesions of the heart and aorta are

TABLE 2—*Percentage Incidence of Cardiovascular Syphilis by Race and Sex Among 6,420 Patients with Late Syphilis (After Turner)*

Cardiovascular Condition	Percentage Incidence				
	Total	White Patients		Colored Patients	
		Male	Female	Male	Female
Aneurysm of aorta	12	12	03	30	07
Aortic regurgitation	27	28	14	50	15
Other forms of cardiovascular syphilis	62	47	31	99	50
Total incidence*	101	72		114	

* The percentage of incidence of cardiovascular syphilis in the total number of males was 13.9, in the total number of females, 6.7.

so rare as to be negligible. The rates of incidence for aneurysm of the aorta and aortic regurgitation, which form the subject matter of this paper, are given separately. The caption "other forms of cardiovascular syphilis" includes uncomplicated syphilitic aortitis, angina pectoris, myocarditis, etc. Aortitis is, of course, the most frequent of these. As Turner pointed out, cardiovascular syphilis is more frequent in males than in females in the proportion of two to one, and more frequent in Negroes than in whites. The Negro male is almost four times as liable to acquire this lesion as the white female. That there is a definite race and sex predilection there can be no doubt. The excessively high rate among colored males is usually attributed to the influence of hard physical labor. That this can hardly be the only explanation is indicated

9 Dublin, L. I. Statistical Aspects of the Problem of Organic Heart Disease, *Am Heart J* 1:359, 1926.

10 White, P. D. Heart Disease, New York, The Macmillan Company, 1931, pp 302-303.

11 Turner, T. B. The Race and Sex Distribution of the Lesions of Syphilis in 10,000 Cases, *Bull Johns Hopkins Hosp* 46:159, 1930.

by the fact that the percentage incidence in colored females (72) is almost equal to that in white males (87)

It is a curious and as yet unexplained statement that cardiovascular syphilis appears to be as uncommon in the African Negro resident in the tropics as it is common in the American Negro (Manteufel,¹² McArthur¹³) Like the lower incidence of neurosyphilis in the tropics, this is usually attributed to the lazy, care-free life of the African Negro, in contrast to the strain of civilization and the hard physical labor to which his American brother is subjected To the skeptic, a much more logical explanation would appear to lie in the almost inextricable confusion of syphilis and frambesia in the tropics, on the one hand, and, on the other, to inadequate clinical study The evidence so far adduced as to the actual absence of cardiovascular lesions in tropical syphilis is unconvincing

TABLE 3—*Race and Sex Incidence of Aneurysm and Aortic Regurgitation in This Series of Patients*

Cardiovascular Condition	Total Number of Cases	Number of Cases in					
		White Males	White Females	Total White Group	Colored Males	Colored Females	Total Colored Group
Aneurysm	53*	12		12	33	8	41
Aortic regurgitation	112	29	10	39	57	16	73
Totals†	165	41	10	51	90	24	114

* In nine, aneurysm was complicated by aortic regurgitation

† Total for males, 131, total for females, 34

The race and sex distribution of the 165 cases of this study is shown in table 3 Drawn from the larger material of table 2, the figures in table 3 of course parallel those in table 2 closely Nine patients with both aneurysm and aortic insufficiency have been classified with the aneurysm group, and this classification is retained throughout the paper

From the pathologic standpoint, the incidence of cardiovascular syphilis, especially of syphilitic aortitis, is vastly higher than the acumen of clinical diagnosis would indicate Careful studies of syphilitic patients at necropsy show that aortitis is present in from 70 (Langer¹⁴) to 90 per cent (Warthin¹⁵) In the majority of these, the lesion must be below the level of clinical recognition In only 39.3 per cent of Langer's patients (including those with simple aortitis, those with aortic regurgi-

12 Manteufel, P Syphilis in den Tropen, in Jadassohn Handbuch der Haut- und Geschlechts-Krankheiten, Berlin, Julius Springer, 1928, vol 17, pt 3

13 McArthur, D C Syphilis in the Bechuanaland Native Some Points Wherein It Differs from That Seen in the European, Brit J Dermat **35** 411, 1923

14 Langer, E Die Häufigkeit derluetischen Organveränderungen insbesondere der Aortitis luetica, Munchen med Wchnschr **73** 1782, 1926

15 Warthin, A S The Lesions of Latent Syphilis, South M J **24** 273, 1931

tation and those with aneurysm) was the condition correctly diagnosed during life. We recently showed² that the diagnosis of uncomplicated aortitis (excluding aortic regurgitation and aneurysm) was correctly made or suspected ante mortem in only 16.2 per cent of 105 patients in whom the lesion was found at necropsy.

Obviously, therefore, every patient with inadequately treated late syphilis must be suspected of having syphilitic aortitis, and in at least

TABLE 4—*Age of Patients with Aneurysm and Aortic Regurgitation in This Series, on Admission to Hospital*

	Total Number of Patients	Number Who on Admission Were of Age Given				
		21-30 Yr	31-40 Yr	41-50 Yr	51-60 Yr	61-70+ Yr
Patients with aneurysm						
White						
Males	12		2	2	4	4
Females						
Colored						
Males	33	3	12	11	7	
Females	8		1	6	1	
Patients with aortic regurgitation						
White						
Males	29	3	5	11	8	2
Females	10		3	3	4	
Colored						
Males	57	2	22	19	14	
Females	16	4	7	4	1	
Total						
White	51	3	10	16	16	6
Colored	114	9	42	40	23	
Males	131	8	41	43	33	6
Females	34	4	11	13	6	

TABLE 5—*Average Age of Patients with Aneurysm and Aortic Regurgitation, on Admission to Hospital*

Diagnostic Group	Average Age, Years					Total Colored Group
	White Males	White Females	Total White Group	Colored Males	Colored Females	
Patients with aneurysm (46 yr)	53		53	42	45	43.5
Patients with aortic regurgitation (43 yr)	46	46	46	44	40	42
Totals*			48			42

* Average age of total number of males, 45 years, females, 41 years

7 of every 10 cases this suspicion will be verified at necropsy. Equally obviously, the situation is not so serious as this from the clinical standpoint. Many of the pathologic diagnoses of syphilitic aortitis are based on the finding of microscopic lesions in the aortic wall which are not only below the threshold of clinical recognition but also below that of marked physiologic disturbance. The diagnostic issue must be met by careful and reasonably frequent periodic reexamination of all syphilitic patients and by the routine use of fluoroscopic and teleroentgenographic examination of all patients with late syphilis, in order to detect the presence of aortitis at the earliest possible moment. Here, as in the

diagnosis of syphilis itself, the most successful clinicians will be those who possess what Stokes aptly termed a "high index of suspicion"

AGE OF PATIENTS WITH CARDIOVASCULAR SYPHILIS

In table 4 is shown the age on admission of the 165 patients in this series. It is interesting to note that both aneurysm and aortic regurgitation tend to appear at a later age in white males than in other groups. For example, 68 per cent of the white males with aneurysm and 34 per cent of those with aortic insufficiency were over the age of 50, while,

TABLE 6—*Duration of Infection with Syphilis in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Total Number of Patients	Number Whose Infection on Admission Was of Duration Given										
		0-5 Yr	6-10 Yr	11-15 Yr	16-20 Yr	21-25 Yr	26-30 Yr	31-35 Yr	36-40 Yr	41-45 Yr	46-50 Yr	Duration Unknown
Patients with aneurysm	53		3	6	9	3	4	2	2	1		2
Patients with aortic regurgitation	112	2	5	9	18	10	3	4	3			58
Total	165	2	8	15	27	13	7	6	5	1		81

TABLE 7—*Average Duration of Infection with Syphilis in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Average Duration, Years					
	White Males	White Females	Total White Group	Colored Males	Colored Females	Total Colored Group
Patients with aneurysm (21 yr)	24			20	(Insufficient data)	
Patients with aortic regurgitation (20 yr)	21	(Insufficient data)		19	(Insufficient data)	
Total*		(Insufficient data)	22		(Insufficient data)	20

* The average duration of infection in the total number of males was 20 years

of Negro males with these conditions, only 20 per cent and 24 per cent, respectively, were over the age of 50. Forty-five per cent of the Negroes were affected before the age of 40, while only 25 per cent of the whites were affected before this age. The majority of the cases occur, as has been repeatedly shown, in the fifth decade of life.

The same data, summarized and rearranged, appear in table 5. Here it is again shown that with both types of lesion, whites are affected later in life than Negroes and males later than females. The explanation of this observation is not clear. That physical stress plays any part seems unlikely, since the youngest group to be affected is that of Negro females. Duration of infection with syphilis may be the responsible factor.

DURATION OF INFECTION AND CARDIOVASCULAR SYPHILIS

Data bearing on this point are presented in table 6 and are summarized in table 7. In almost half the cases no history of early syphilis was obtainable. This was true of most of the women and a few of the men. In 2 patients, aortic regurgitation developed within the first five years of the infection. Sixty-five per cent of the cases occurred between the eleventh and twenty-fifth years of the infection. There is no perceptible difference between the aneurysm and aortic regurgitation groups. The summary in table 7 shows that cardiovascular syphilis tends to develop sooner in Negro males than in white males, and that aortic regurgitation tends to appear in both races a little earlier than aneurysm. These figures suggest that cardiovascular syphilis develops in Negroes at an earlier age than in white patients because they are infected earlier in life. The average age at infection of the two groups in this series is

TABLE 8—*Duration of Symptoms on Admission (Prior to Treatment) in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Total Number of Patients	No Who Had No Symptoms*	Number with Duration of Symptoms Given							No on Whom No Data Were Obtained
			1 12 Wk	4 6 Mo	7 9 Mo	10 12 Mo	1 2 Yr	2 3 Yr	3+ Yr	
Patients with aneurysm	53	9	12	14	7	4	2	3	1	1
Patients with aortic regurgitation	112	11	36	15	7	12	8	8	6	9
Total	165	20	48	29	14	16	10	11	7	10

* These patients had had no symptoms indicating cardiovascular damage. The lesion was discovered during routine physical examination.

22 and 26, respectively. No adequate data are available for the duration of infection in females of either race.

DURATION OF SYMPTOMS OF CARDIOVASCULAR SYPHILIS

The data showing the duration of symptoms on admission to the clinic and before the institution of treatment are presented in table 8. In 9 patients with aortic aneurysm and 11 with aortic regurgitation there had been no symptoms of any sort pointing to cardiovascular damage. Each of these 20 patients came to the hospital for some other reason, and the lesion was discovered in the course of routine physical examination. No stronger evidence could be presented of the necessity for thorough examination of all patients with syphilis. In the majority of patients, the onset was relatively abrupt, with dyspnea on exertion, paroxysmal nocturnal dyspnea, pain or even the sudden onset out of an apparently clear sky of congestive heart failure. Such patients quickly sought relief. Not infrequently, however, the onset was insidious and slowly progressive, and in 28 patients (6 with aneurysm and 22 with aortic regurgitation) symptoms had existed for more than a year before the patient came to the hospital. Here the usual story was one of the gradual

appearance of slight exertional dyspnea, which only slowly became more marked or associated with other more alarming symptoms. We have no information as to the extent to which these patients had consulted other physicians before coming to the Johns Hopkins Hospital, but we have the impression that this was not frequent.

From our material nothing can be said as to the time of appearance of physical signs as related to symptoms, age or duration of infection. In all of our patients, characteristic physical signs were present at the time of admission. To answer this question would necessitate the careful following up of a large series of patients with early syphilis over a long period of years.

SOCIAL STATUS AND OCCUPATION

Four patients in this series were from the private practice of one of us (J. E. M.), the remainder were from the semifree clinic of the

TABLE 9—*Other Lesions of Syphilis Associated with Aneurysm and Aortic Regurgitation*

Cardiovascular Condition	Total Number of Cases	No. in Which Some Other Lesion of Syphilis Was Present	Number in Which the Other Syphilitic Lesion Was of Type Given				
			Central Nervous System	Bone	Skin	Eye	Other
Aneurysm	53	15	9 (2 tabes, 1 dementia paralytica, 2 asymptomatic, 4 meningovascular)	2	4	1	
Aortic regurgitation	112	29	20 (8 tabes, 3 asymptomatic, 3 vascular, 6 meningovascular)	7	2		1 (gumma of larynx)

Johns Hopkins Hospital. Of the 131 males, all except 12 had been engaged in some occupation that demanded considerable physical exertion, and all of the females except one had done their own housework. Only general statements can be made as to the physical and constitutional status of our patients. Except for the presence of cardiovascular syphilis and its complications, most of them appeared to be in remarkably good physical condition. Associated diseases not due to syphilis were uncommon. Most of the men were finely developed muscular persons, apparently in the prime of life.

COINCIDENT SYPHILIS OF OTHER ORGANS

The frequency with which these patients with cardiovascular syphilis were also affected by other syphilitic lesions is shown in table 9. Here is reemphasized the frequent association, so often pointed out, of syphilis of the cardiovascular apparatus and syphilis of the nervous system. Seventeen per cent of the patients with aneurysm and 18 per cent of

those with aortic regurgitation had coincident clinical evidence of neurosyphilis. Curiously enough, late cutaneous lesions occurred in 75 per cent of the group with aneurysm but in only 17 per cent of the patients with aortic regurgitation, while the reverse relationship was true for late osseous syphilis, which occurred in 37 per cent of the group with aneurysm and in 62 per cent of that with aortic regurgitation. It is probable that these relationships are only apparent, depend on the relatively small number of cases involved and have no real statistical significance.

THE WASSERMANN REACTION OF THE BLOOD AND THE CEREBROSPINAL FLUID IN CARDIOVASCULAR SYPHILIS

In table 10 appear the figures dealing with the Wassermann reaction of the blood and with the cerebrospinal fluid of the patients under consideration. Of the patients with aneurysm, 98.1 per cent, and of those

TABLE 10—*The Wassermann Reaction of the Blood and the Results of Tests of the Cerebrospinal Fluid in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Total Number with Data on Wassermann Reaction Available	Number with Wassermann Reaction of the Blood as Given			Total Number with Data on Cerebrospinal Fluid Available	Number with Reaction of Cerebrospinal Fluid as Given	
		Positive	Doubtful	Negative		Positive	Negative
Patients with aneurysm	52	50	1	1	20	8	12
Patients with aortic regurgitation	111	102	5	4	52	11	41
Total	163	152	6	5	72	19	53

with aortic regurgitation, 96.4 per cent, had a positive Wassermann reaction of the blood. As Carter and Baker⁸ pointed out in their survey of similar patients drawn from the same hospital but from a different service, these figures are in excess of many published statistics.

The spinal fluid of our patients with cardiovascular syphilis has not been tested as a routine as has that of our patients with other types of late syphilis. In many instances we have felt that the patient was so ill from his cardiovascular lesion that, whether or not he showed clinical evidence of neurosyphilis, it was unnecessary and unjustifiable to inflict on him the added discomfort of lumbar puncture. The figures shown in table 10 have therefore no real significance, except as they corroborate the clinical diagnoses of neurosyphilis shown in table 9. Elsewhere we have published¹⁶ data showing that the incidence of

¹⁶ Moore, J. E., and Faupel, Mildred. Asymptomatic Neurosyphilis. V. A Comparison of Early and Late Asymptomatic Neurosyphilis, *Arch. Dermat. & Syph.* 18:99 (July) 1928.

abnormal spinal fluids in 94 patients with cardiovascular syphilis, but without any clinical evidence of involvement of the central nervous system, was 17 per cent. A reasonably accurate estimate of the incidence of neurosyphilis complicating cardiovascular syphilis may be set at from 30 to 35 per cent, by adding the percentage for asymptomatic neurosyphilis (17 per cent) to the percentage of patients in the present series with associated clinical neurosyphilis (17 per cent). Stokes,¹⁷ in his admirable chapter covering a survey of 200 white patients with cardiovascular syphilis, reported that 49 per cent of them had clinical signs of neurosyphilis, and that an additional 5 per cent had abnormal spinal fluids but no signs. Thus, almost one third to one half of all patients with cardiovascular syphilis show clinical or serologic evidence of associated involvement of the nervous system. It may be mentioned in passing that the reverse relationship is still more frequent in certain types of neurosyphilis. Thus, while not all patients with cardiovascular syphilis have tabes, practically all tabetic patients have syphilitic aortitis.

ASSOCIATION OF CARDIOVASCULAR SYPHILIS AND NEUROSYPHILIS AS A COMPLICATING FACTOR IN TREATMENT

The frequent association of cardiovascular syphilis and neurosyphilis often complicates the problem of treatment. One may be hard put to it to decide which is the more important from the patient's point of view. Given, for example, the association of dementia paralytica or tabes dorsalis with optic atrophy and cardiovascular syphilis, to what extent is one justified in subjecting the patient to treatment which is adequate to restore sanity or to prevent or delay loss of vision but which may hasten death from the cardiovascular lesion? Each case is a problem to be decided on its merits. Recently, one of us (J. E. M.) was confronted with the problem of treatment of a private patient with tabes and dementia paralytica (not included in this series) with a manic-grandiose psychosis, rapidly progressing bilateral optic atrophy, syphilitic aortitis with aortic regurgitation, chronic nephritis, hypertension (200 systolic and 120 diastolic), beginning cardiac decompensation and a history of severe postarsphenamine exfoliative dermatitis. The patient's only chance of recovery from the dementia paralytica appeared to lie in fever therapy, tryparsamide being contraindicated because of the optic atrophy. After preliminary digitalization and apparent recovery of cardiac compensation, he was inoculated with malaria. This had to be terminated after six paroxysms because of a rapidly rising nonprotein nitrogen and impending uremia, but after an

¹⁷ Stokes, J. H. *Modern Clinical Syphilology*, Philadelphia, W. B. Saunders Company, 1926, p. 818.

interval of three weeks, during which these complications disappeared, he was reinoculated and nursed safely through six more paroxysms. Within a month after treatment, he had a complete remission so far as the psychosis was concerned. He was able to leave the psychiatric hospital in which he had been confined, and it is now possible to undertake the further treatment for the cardiovascular features of his illness with measures that would have been utterly ineffective for the neurologic manifestations.

Usually, however, one is faced with a less serious problem, in that the choice of a method of therapy is less for the purpose of dealing with two manifestations of syphilis, either of which will surely be fatal

TABLE 11—*Type and Amount of Antisyphilitic Treatment Received by Patients with Aneurysm and Aortic Regurgitation Prior to Development of Cardiovascular Syphilis*

Diagnostic Group	Total Number of Patients	Number with History of Infection with Syphilis	Number with No History of Infection with Syphilis	Number Who Had No Treatment for Syphilis Prior to Onset of Cardiovascular Lesion	Number Who Had Had Treatment for Given Type of Syphilis Prior to Onset of Cardiovascular Lesion			
					Early Syphilis (No Arsphenamine)	Early Syphilis (Treatment Included Arsphenamine)	Late Syphilis (Treatment Inadequate)	Late Syphilis (Treatment Adequate)
Patients with aneurysm	53	30	23	48	3	1	1	
Patients with aortic regurgitation	112	54	58	99	8	3		2
Total	165	84	81	147	11*	4†	1	2

* In two cases, the administration of mercury (by rubs or by mouth) was continued for from two to three years, in all others, for a few weeks or months only.

† In these cases, the number of injections of arsphenamine for early syphilis was from one to three.

without treatment, than for that of accomplishing the amelioration of distressing symptoms of neurosyphilis by a scheme of treatment that will also be of benefit from the cardiovascular standpoint. Tryparsamide or intraspinal treatment with heterologous arsphenamized serum can sometimes be employed without added risk and with considerable benefit. An intensification of arsphenamine therapy past the point advisable from the standpoint of the circulatory apparatus calls for the most searching scrutiny and careful observation of the patient.

RELATIONSHIP OF PREVIOUS ANTISYPHILITIC TREATMENT TO DEVELOPMENT OF CARDIOVASCULAR SYPHILIS

We have pointed out that reasonably adequate treatment for early syphilis appears to protect the patient against a subsequent development of cardiovascular syphilis. In table 11, we approach this important ques-

tion from another angle, that of the amount of treatment for syphilis received by the patients in this series before the development of cardiovascular damage. For the sake of completeness, we reemphasize the fact that only 30 of the 53 patients with aneurysm and 54 of the 112 with aortic regurgitation gave any history of possible early manifestations of the infection. Practically all of the remaining 81 patients (49 per cent) had no idea that they had syphilis until the diagnosis was made at the time of their admission to the hospital for cardiovascular syphilis. This includes almost all of the 34 women in the series, and also a large number of the men. Stokes,¹⁷ dealing with an exclusively white clientele, found that one third of his 200 patients with cardiovascular syphilis could give no history of infection. Symptomless infection, now demonstrated in animals,¹⁸ or infections with insignificant chancres and an absent or unobtrusive secondary outbreak, must be nearly as common in patients in whom cardiovascular syphilis subsequently develops as in those who fall victims to neurosyphilis. In any large series of patients with cardiovascular syphilis, therefore, one can expect that from one third to one half of the patients will never have received any previous treatment, because they will have been unaware that they were infected.

It is startling to note, however, that in our material only 15 of the 84 patients who gave a history of early syphilis had ever taken any treatment for it. Of these, 11 had had only mercury, and only 2 of the latter group had continued this form of therapy for what was felt, in the prearsphenamine days, to be an adequate length of time. Nine had taken the drug for a few weeks or months only, stopping because they thought themselves cured. Four patients had received from one to three injections of an arsphenamine product at the time of their infection. Not a single patient in this whole series had received as many as six injections of arsphenamine for early syphilis. These figures are in striking corroboration of the opinion that adequate early treatment prevents the development of cardiovascular damage. Three additional patients had been treated before their admission for neurosyphilis, the cardiovascular lesion either having been overlooked or having subsequently developed. Two of these had received as many as two courses of treatment with arsphenamine with interim treatment with heavy metal compounds.

One hundred and forty-seven patients (89 per cent) had never received treatment for syphilis.

These data, with the figures given in an earlier paragraph as to the incidence of cardiovascular syphilis in patients receiving varying amounts

18 Kollé, W. Ueber symptomlose Infektionen und ihre Bedeutung für Epidemiologie, Pathologie, und Immunität, insbesondere der Syphilis, *Schweiz med Wchnschr* 59 517, 1929

of treatment for early syphilis at our hands, have an important bearing on the controversy taking place, especially in Germany, over the apparently increased incidence of syphilitic aortitis since the introduction of arsphenamine. Langer's important paper¹⁴ provides a discussion of this disputed point. He and others concluded that there has been a striking increase in the incidence of syphilitic aortitis as observed at necropsy during the past fifteen years. Our material indicates, first, that the vast majority of all patients with cardiovascular syphilis have never been previously treated, second, that a relatively small amount of arsphenamine appears to protect the patient against the development of cardiovascular damage. Our feeling is that the increased incidence is more apparent than real and is based on increasingly accurate pathologic study and a more intimate knowledge of the microscopic lesions of syphilitic aortitis.

THE LITERATURE ON THE TREATMENT OF CARDIOVASCULAR SYPHILIS

We have not attempted a detailed review of the literature on the treatment for cardiovascular syphilis, chiefly because there are few reports with the material of which ours may be compared. It is difficult, if not impossible, to obtain from the older literature any clear idea of how often or to what extent actual benefit occurred. Most writers on the subject (and this criticism applies also to the more modern writers) discuss the prognosis and outcome in "cardiovascular syphilis" or in "syphilitic aortitis" without differentiating the clinical material further. Obviously, the prognosis and the results to be expected from treatment should be better in the stage of simple aortitis than after the development of aortic insufficiency or of aneurysm, and in the latter two conditions, better before than after the appearance of manifest myocardial failure. Many of the older clinicians, and more recent authors as well, advocate one or another method of treatment, or advise against treatment, on the basis of their opinions, failing to detail the facts on which their opinions are based. Others describe the results of treatment in a small number of cases. To draw conclusions from individual instances of apparent therapeutic success or failure, or to consider a few cases only, no matter how carefully studied, is a dangerous procedure in a condition in which progress without treatment is so variable as in cardiovascular syphilis. The only fair method of approach to the problem is by the statistical study of a larger number of comparable cases.

We have been able to find four papers in which data are presented in some degree comparable with our own. In 1919, Reid¹⁹ reported the results of treatment in 61 patients with syphilitic aortitis, of whom 43

¹⁹ Reid, W. D. Prognosis of Specific Aortitis, *J. A. M. A.* **73** 1832 (Dec. 13) 1919.

presumably had aortic regurgitation. He was able to follow only 22 of these patients, but concluded that with proper treatment symptoms were alleviated and life definitely prolonged. It is not possible to be sure how many of his followed patients had simple aortitis or aortic insufficiency, and the numbers involved are too small for statistical accuracy as to prolongation of life.

Cotton,²⁰ in 1926, discussed the ultimate outcome in 107 patients with aortic regurgitation, of whom 7 also had aortic aneurysm. Fifty-two of this group were given no antisyphilitic treatment and were used as controls. The remaining 55 were treated with courses of neoarsphenamine and mercury. The author is not clear as to how much treatment was given, though it is implied that all of the treated patients received a course of each drug once a year for five years. He said that both the untreated and the treated groups were given the same type of general medical care, and that they were observed over a five year period. Presumably, at the end of this period, 34 of the 52 untreated patients were still living and 18 were dead, a mortality of 34 per cent. Of the 55 treated patients, 41 were still living and 14 dead, a mortality of 25 per cent. Thus treatment appeared to offer a 9 per cent increased chance of survival for the period of observation. It is unfortunate that Cotton did not define more accurately the duration of life in treated and untreated patients. On the basis of our own material and that of other observers the world over, it is difficult to believe that 34 of the 52 untreated patients with aortic regurgitation survived for a full five years, since it is generally agreed that the average duration of life after the onset of symptoms in untreated patients with aortic regurgitation is from one to two years (Scott).²¹ The value of Cotton's paper is much impaired by this omission and by his failure to provide more accurate details of the treatment given.

Conybeare²² reported on the effect of treatment in aortic aneurysm. His series was small, consisting of only 23 patients, but his data are well presented. Twelve patients, serving as controls, received no antisyphilitic treatment. Of these, 4 were living at the time of the report, the average duration of life from the onset of symptoms being forty-five months, 8 were dead in an average period of ten months. Eleven patients were treated with varying amounts of neoarsphenamine. Only 2 of these received much treatment, the remaining 6 all being given from one to eight injections of the drug. In spite of this relatively

20 Cotton, F F Cardioaortic Syphilis and Its Treatment, *Brit M J* **1** 855, 1926

21 Scott, R W Syphilitic Aortic Insufficiency, *Arch Int Med* **34** 645 (Nov) 1924

22 Conybeare, J J The Treatment of Aortic Aneurysm by Anti-Syphilitic Remedies, *Guy's Hosp Rep* **74** 163, 1924

small amount of treatment, 7 of the treated patients were still living over an average period of forty months from the onset of symptoms, and 4 of these were symptom-free and able to do hard physical labor. Four were dead in an average period of thirty months. On the basis of these figures, Conybeare was convinced of the value of neoarsphenamine in aortic aneurysm.

Recently, Herrmann and Jamison²³ discussed the outcome of treatment in 100 patients with aortic regurgitation, all of whom had had congestive heart failure before treatment was started. Unfortunately, these authors subdivided their material into small groups and attempted a simultaneous but not interrelated analysis of the effect of varying amounts and types of antisyphilitic treatment and the effect of such various measures to relieve congestive heart failure as ouabain, large versus small doses of digitalis, etc., so that it is difficult, if not impossible, for the reader to unravel the significance of their figures. Disregarding all features of their report except that dealing with antisyphilitic treatment, and rearranging their figures for the sake of simplicity, one finds that 40 patients received little or no treatment, of whom 12 were living and 28 dead at the date of reporting, a mortality of 70 per cent. Fifty-eight patients were given what we should regard as a moderate amount of treatment (corresponding roughly to the treatment given our groups 2 and 3, subsequently to be described), of these, 26 were living and 32 dead, a mortality of 55 per cent. It is impossible to extract from this paper any quotable details as to the average duration of life in the various groups. The authors concluded, however, that antisyphilitic treatment definitely prolongs life, and that, while living, treated patients are usually much more comfortable than those who are untreated. Herrmann and Jamison properly laid great stress on the prognostic importance of congestive heart failure and the necessity for adequate supportive treatment from the standpoint of the circulation.

EVOLUTION OF A METHOD OF TREATMENT FOR CARDIOVASCULAR SYPHILIS

The past twenty years have seen three almost complete revolutions in the attitude of physicians toward the treatment for cardiovascular syphilis. Before the introduction of arsphenamine, it was generally agreed that some benefit could be obtained from the judicious use of mercury alone, mercury with iodides or the iodides alone. Symptomatic improvement occurred often with a combination of these treatments,

²³ Herrmann, G., and Jamison, C. The Treatment of Cardiovascular Syphilis with Especial Reference to Aortic Regurgitation with Congestive Heart Failure. *Am J Syph* 15 1, 1932.

and many able clinicians were convinced that, at least in individual cases, life was prolonged

After the introduction of arsphenamine, and in spite of the original cautions against its use in patients with damaged hearts, it was almost as universally applied to the treatment of patients with syphilitic heart disease as to the treatment of those with late syphilis of all types. At this point, our experience in the management of cardiovascular syphilis began. The results of this indiscriminate use of a powerful drug were disastrous. It was found that when the drug was given in average therapeutic dosage to ambulant patients, sudden death might occur during the injection. Such reactions were characterized by fainting, ashy gray-green pallor and profuse sweating, the pulse became rapidly imperceptible, the patient gave a few gasps and died. At least four such deaths occurred in our own clinic.

Electrocardiographic studies by Reid²⁴ and by Wilson, Wile, Wishart and Herrmann²⁵ have an important bearing on the mechanism of this type of reaction. Each of these observers gave arsphenamine in average therapeutic doses (from 0.3 to 0.4 Gm.) to patients with syphilitic heart disease, obtaining electrocardiographic records before and shortly after the injection. Reid observed changes that he interpreted as a prolongation of conduction time and a shortened refractory period of the muscle. He concluded that in a heart which is damaged by syphilis, and which is in "a bad metabolic state," these two changes predispose to the occurrence of ectopic ventricular tachycardia or to ventricular fibrillation, the latter of which is, of course, suddenly fatal. Wilson and his co-workers likewise noted abnormal idioventricular rhythm and diphasic complexes suggesting incomplete bundle branch block, and concluded that, in cardiovascular syphilis, the administration of arsphenamine may sometimes be followed by myocardial changes of an undesirable kind.

A second type of disastrous outcome was sudden death within from twenty-four to forty-eight hours after the injection of the drug, due to therapeutic shock (Jaisch-Herxheimer reaction). Usually this was due to sudden coronary occlusion or to rupture of an aneurysm. Still a third untoward effect was the sudden appearance of congestive heart failure in patients whose cardiac compensation had been adequate before treatment. This was emphasized by Wile²⁶ as "the therapeutic paradox."

24 Reid, W. D. The Mechanism of the Toxic Action of Arsphenamine on the Heart, *J. A. M. A.* **84** 883 (March 21) 1925.

25 Wilson, F. N., Wile, U. J., Wishart, S. W., and Herrmann, G. R. Changes in the Electrocardiogram Following the Arsphenamine Treatment of Cardiac and Aortic Syphilis, *Proc. Soc. Exper. Biol.* **23** 275, 1926.

26 Wile, U. J. The Treatment of the Syphilitic Liver and Heart. A Therapeutic Paradox, *Am. J. M. Sc.* **164** 415, 1922.

He attributed the phenomenon to the rapid healing of syphilitic inflammatory tissue in the aortic wall, valve cusps or myocardium, which is then replaced by contracting scar tissue. This brings about anatomic healing, but leaves the patient functionally worse than before treatment. The early current favorable opinion as to the beneficial effect of treatment with arsphenamine, summarized by Longcope,²⁷ was more than counterbalanced by the ill effects just described.

For a time, the pendulum swung back, and it was generally thought that, since the danger of treating patients with cardiovascular syphilis was far greater than the improvement to be expected, it was better to give no antisyphilitic treatment or, if any, mercury and potassium iodide only, as in the prearsphenamine era. We shared in this feeling of pessimism, and for several years our patients received no treatment other than the usual medical measures of rest, diet, digitalization and restriction of activity. Patients so treated constitute a large part of our control material, shortly to be described.

The World War was partly responsible for the inauguration of the plan of treatment of persons with cardiovascular syphilis which we now employ, and which, subject to various modifications, has been independently evolved by many other observers.²⁸ Neoarsphenamine became popular during the war years because of its ease of administration. It was found to be less prone to produce minor reactions in average therapeutic doses than arsphenamine and in small dosage to be practically free from any after-effect. This led to its trial cautiously in patients with cardiovascular syphilis, and it was generally found that with proper precautions such patients could tolerate small doses (from 0.1 to 0.3 Gm.) without the dangers of sudden death from ventricular fibrillation or from therapeutic shock. The measures taken to avoid the latter disaster, namely, several months of preliminary treatment with mercury and the iodides in order to promote slow rather than rapid resolution

27 Longcope, W. T. Syphilitic Aortitis. Its Diagnosis and Treatment, *Arch Int Med* **11** 15 (Jan) 1913.

28 Braun, L. Ueber die Behandlung der syphilitischen Herz- und Gefasskrankheiten, *Wien med Wchnschr* **77** 122 and 150, 1927. Goldberg, B. I. The Value of Specific Treatment in Cardiovascular Syphilis, *Boston M & S J* **193** 768, 1925. Herrmann and Jamison (footnote 23). Hines, L. E., and Carr, J. G. The Use of Intravenous Arsenicals in the Treatment of Cardiovascular Syphilis, *Am Heart J* **6** 142, 1930. Horder, T. Syphilis of the Heart and Aorta and Its Appropriate Treatment, *Brit J Ven Dis* **2** 117, 1926. Scherber, G. Die Behandlung der verschiedenen Formen der syphilitischen Mesoartitis, *Dermat Wchnschr* **92** 56, 1931. Schlesinger, H. Die Behandlung der Mesoartitis im Stadium der Dekompensation, *Wien klin Wchnschr* **43** 562, 1930. Schottmuller, H. On the Treatment of Syphilis of the Aorta, *Am J Syph* **9** 1, 1925. Stokes (footnote 17, p. 850). Symposium (Citron, Galewsky, Kisch, Leschke, Ritter, Schlesinger). Indikationen und Erfolge der spezifischen Therapie bei Aorten Syphilis, *Dermat Wchnschr* **92** 19, 1931.

of syphilitic inflammatory tissue, were also found to be of value in preventing the therapeutic paradox. The introduction of bismuth provided another drug free from dangerous after-effects and therapeutically more active than mercury. From the accumulated experience with the use of these drugs, in combination with the older medical measures, has evolved the rather elastic treatment scheme which we now describe.

If, on admission, the patient has any evidence of congestive heart failure, he is promptly put at complete rest in bed and is digitalized. Diet and fluid intake are restricted. If there is no edema, antisyphilitic medication, except for the iodides, is omitted until compensation has been regained. If edema is present, one of the soluble mercurial salts (for example, succinimide intramuscularly or salyrgan intravenously) may be employed for a few days for its combined diuretic and antisyphilitic effect. As Brooks²⁹ and also Carter and Baker⁸ pointed out, patients with cardiovascular syphilis, especially Negroes, seem to be more refractory to digitalis than those with other forms of cardiac failure, and even large doses sometimes fail to produce any physiologic effect. Rest in bed is prolonged, if possible, until well after compensation has been recovered, convalescence is purposely slow, and graduated exercise is rigorously supervised. On discharge from the hospital, restriction of activity is insisted on, often necessitating a change of occupation from manual labor to a sedentary position requiring a minimum of physical exertion. The patient is warned against sudden physical strain of any type. Powdered digitalis, in a dosage of from 0.1 to 0.2 Gm daily, is given to ambulant patients with a low cardiac reserve over indefinite periods of time, sometimes continuously. For anginal pains or substernal discomfort, the nitrites and a mixture containing theobromine and phenobarbital have proved helpful. Careful watch is kept for an impending repetition of cardiac failure, and if symptoms appear, rest in bed is immediately reinstituted. Encouragement is essential, and it is often wise to conceal the gravity of the situation from the patient, at the same time notifying a responsible member of the family of a possible unfortunate outcome.

Antisyphilitic treatment, usually with intramuscular injection of an insoluble bismuth salt combined with the administration of potassium or sodium iodide by mouth, is started as soon as a fair degree of cardiac reserve has been established. The dosage of bismuth is usually small at first—0.1 Gm every four or five days. If this is tolerated for four or five injections without an upset, as is ordinarily the case, the dose is increased to 0.2 Gm once a week. At the start of treatment, we believe that insoluble bismuth salts are preferable to soluble salts, because of their slower absorption, and preferable to mercury by any route because

29 Brooks, H. The Treatment of Cardiovascular Syphilis, Warthin Anniversary Volume, Ann Arbor, Mich., George Wahr, 1927, p. 117.

of their lower toxicity and more certain therapeutic effect. The dosage of the iodide is usually 1.3 Gm three times a day, increasing rapidly to 4 Gm three times daily. Larger doses than these appear to be unnecessary. This type of treatment with bismuth and the iodides is continued for at least from ten to twelve weeks before any arsphenamine product is given. Indeed, in some patients who never succeed in establishing a satisfactory degree of cardiac reserve, the use of any arsenical drug is omitted, and treatment carried on with courses of bismuth and the iodides alternating with rest periods of from two to four months, or with courses of mercury by inunction. If, on completion of the first course of bismuth, the patient has not sufficiently recovered compensation as to be completely ambulatory without the persistence of slight edema or some exertional dyspnea, the arsenical drug of choice is bismarsen (bismuth arsphenamine sulphonate). This preparation is administered intramuscularly in a dosage of first from 0.05 to 0.1 Gm not oftener than every five days, and later, if no reactions occur, 0.2 Gm every four to seven days. A course of bismarsen consists of from twelve to twenty injections. If, on the other hand, the patient is able to be ambulatory with only slight or no symptoms of cardiac embarrassment, neoarsphenamine administered intravenously, is employed. The initial dosage is again minute, from 0.05 to 0.1 Gm, and is cautiously increased at weekly intervals and by gradual steps until the usual maximum dose of 0.3 Gm is reached. In rare instances, when patients are symptomless, this maximum may be exceeded, and 0.45 or 0.6 Gm given. The aim of treatment is, however, to avoid reactions of any kind, hence the larger dosage of neoarsphenamine, and the use of old arsphenamine particularly, are avoided. A course of neoarsphenamine consists of from ten to twelve injections. Whenever possible, treatment is continued by this system of courses of bismuth and the iodides alternating with courses of neoarsphenamine in small dosage, without rest periods of any kind, for an indefinite period of time, and certainly for a minimum of two years. After two years of continuous treatment, if the patient's general physical condition is satisfactory, it is permissible to institute long periods of rest. It is probably wise to give an occasional course of bismuth followed by one of bismarsen or neoarsphenamine, say perhaps once a year, for the duration of the patient's life. The minimum requirement of two years of treatment has been arbitrarily set, based on the clinical progress of the patients reported on in this paper. No attention is paid to the response of the Wassermann reaction of the blood to treatment, since Wassermann fastness is the rule.

Whether it is advisable to attempt this treatment régime or to limit one's self to medical measures for the relief of symptoms only depends on many collateral factors, such as age, general physical con-

dition and presence of a complicating disease Six patients in the present series were over the age of 60, and recently we have seen 2 patients, aged 72 and 81, respectively, in whose cases the diagnosis of syphilitic aortic regurgitation seemed certain Here it is obviously undesirable to do much more than to give mercury by mouth The presence of severe impairment of renal function may preclude the use of mercury or of bismuth in any form, and one's sole reliance must be placed on bismarsen or on neoarsphenamine

Complicating neurosyphilis, especially tabes dorsalis or dementia paralytica, may call for special measures of treatment, including the use of tryparsamide, which fortunately seems to exercise no deleterious effect on the cardiovascular lesion, of intraspinal therapy (usually with heterologous serum) for the relief of optic atrophy or intractable lightning pains or, in desperate situations, of fever therapy Wile³⁰ advocated tryparsamide instead of any of the arsphenamines in selected cases of cardiovascular syphilis, whether or not a complicating neurosyphilis is present He expressed the belief that it may exercise a direct beneficial effect on the cardiovascular lesion As we shall subsequently indicate, we disagree with this point of view, and think that this drug is of little or no value in any type of syphilis except that in which there is involvement of the central nervous system Each patient presents a problem differing from that of every other, and there is no field of syphilotherapy in which the art of medicine needs to be exercised so much as in cardiovascular syphilis

With this general statement of principles of treatment, we proceed to a consideration of the results obtained in the 165 patients comprising the material of this paper Limitations of space prevent any consideration of individual cases, our results must be presented entirely in statistical form Indeed, as we have emphasized, this is the only satisfactory method of presentation, since the course of the disease in any individual patient is so variable as to make conclusions untrustworthy

THE METHOD OF STUDY

The files of the Syphilis Division include the records of a few more than 300 patients with aneurysm or aortic regurgitation Those patients who had disappeared from observation were written to and visited by social service workers When located, they were urged to return to the clinic for examination or, when this was impossible, to provide detailed information as to their present state of health Reports of death were obtained from family physicians, relatives or neighbors, from the files of the Johns Hopkins Hospital, the Municipal Hospital

30 Wile, U J Principles Underlying the Treatment of Cardiovascular Syphilis, *Am Heart J* 6 157, 1930

and the five largest of the other hospitals in Baltimore, and by an examination of the death certificates at the Baltimore City Health Department. The study was completed on July 1, 1931. By that date, it had been possible to trace the ultimate outcome in 165 patients, or more than half of those whose records were in the files. One hundred and nine of these were dead, of the remainder, all were still under observation on July 1, 1931, except 3. These are included in the series and classified as living because they were followed for periods of time ranging from six to eleven years and were living and in good condition when last seen.

In this paper, we review and augment the data as to ultimate outcome in terms of "living and dead" presented in our preliminary paper. At the same time, we have analyzed the material from several other standpoints that we hope will aid in an understanding of what treatment actually accomplishes.

RESULTS OF TREATMENT IN PATIENTS WITH AORTIC ANEURYSM

In table 12 are presented the data as to the effect of treatment on the prolongation of life in 53 patients with aneurysm of the aorta. Nine of these patients also had aortic regurgitation. In all instances except one, the diagnosis was based on physical signs and on the presence of a characteristic sacculated aneurysm of the thoracic aorta at fluoroscopic and teleroentgenographic examination. The excepted instance was that of a patient with an easily palpable aneurysm of the abdominal aorta, the presence of which was confirmed by exploratory operation. Symptoms, however, were absent in 9 patients, a fact to which subsequent reference will be made.

In table 12 and those following, the patients are divided into four groups on the basis of the amount of treatment received. Group 1 includes those patients who received little treatment or none. "Little treatment" means a few weeks of treatment with mercury (byunction or by mouth), an injection or two of an arsphenamine product or a few injections (less than eight) of bismuth. Group 2 includes patients who received the equivalent of one course of an arsenical drug (from six to eight injections) or one long course (from twelve to sixteen injections) of a heavy metal, either bismuth or mercury. This amount of treatment was usually given over a period of from one and one half to four months. In group 3 are patients who received the equivalent of one long course each of an arsenical drug and of a heavy metal, occupying from four to twelve months' time. Group 4 includes all patients treated for more than one year. This involved a minimum of two long courses each of an arsphenamine product and of a heavy metal or four long courses of a heavy metal alone. Many patients in

this group, however, had been more or less continuously treated for several years, and had received from eight to ten courses each of an arsenical drug and of bismuth or mercury

It is important to note that although the 165 patients studied differed in the amount of antisyphilitic treatment received, they were all treated when necessary by the usual medical régime of rest, diet, digitalis, restriction of activity, etc. In this respect, the patients of our treatment group 1 were as well managed as those in group 4. The only essential difference in the treatment received by the patients in these four groups was in the amount of specific treatment for syphilis. It is perfectly fair, therefore, to attribute any difference observed in course or ultimate outcome to this factor, and to no other.

TABLE 12—*Effect of Treatment on Prolongation of Life in Patients with Aneurysm of the Aorta*

Treatment Group	Number of Patients in Group	Number Living	Number Dead	Average Duration of Life Until Death or Last Observation, Dating from	
				Onset of Symptoms	Start of Treatment
Group 1 Patients with no treatment or very little	22	2	20	19 mo	14 mo
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	10	2	8	51 mo	45 mo
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	6	3	3	67 mo	43 mo
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	15	9	6	75 mo	63 mo

The duration of life is measured as dating (*a*) from the onset of symptoms and (*b*) from the start of treatment, until death or the date of the last observation. This distinction is drawn in order to point out, as will be shown later in another way, that the patients with an unfavorable outcome are not necessarily those who had been ill for the longest time before starting treatment.

The data given in table 12 need no detailed explanation. Of 22 patients who received little or no treatment, 2 are now living and 20 are dead, a mortality of 90 per cent. The average interval of time until death, dating from the onset of symptoms, was only 16 instead of 19 months. The discrepancy between this statement and the table is due to the fact that the two living patients have now lived for 52 and 66 months, respectively, after the onset of symptoms. Had these two patients been treated, one would have been inclined to attribute their

apparent longevity to the effects of treatment, this emphasizes our frequently repeated statement that one can draw no trustworthy conclusions from the behavior of the individual case. In the 20 dead patients in group 1, the duration of life from the onset of symptoms ranged between the extremes of 3 and 43 months. Thirteen of them died within one year. Lucke and Rea³¹ quote several authorities who believed that the duration of life after the clinical recognition of aneurysm varies between 12 and 30 months (no distinction being made between treated and untreated patients).

Contrast this gloomy picture with that of the 15 patients who were treated for more than a year (group 4). Of these, 9 are living and 6 are dead, a mortality of 40 per cent. The average duration of life has

TABLE 13—*Effect of Treatment on Prolongation of Life in Patients with Aortic Regurgitation*

Treatment Group	Number of Patients in Group	Number Living	Number Dead	Average Duration of Life Until Death or Last Observation, Dating from	
				Onset of Symptoms	Start of Treatment
Group 1 Patients with no treatment or very little	57	5	52	30 mo	23 mo
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	16	4	12	23 mo	15 mo
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	14	10	4	46 mo	37 mo
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	25	21	4	64 mo	53 mo

risen from 19 to 75 months from the onset of symptoms. The 9 surviving patients have lived for an average of 88 months; the remaining 6 died at an average of 48 months after the appearance of symptoms. The actual durations of life in the living patients are (to July 1, 1931) 18, 46, 52, 68, 72, 98, 132, 144 and 156 months, respectively; in the dead patients, 12, 23, 48, 72, 87 and 97 months, respectively.

The figures for patients in treatment groups 2 and 3 indicate that even a little treatment aids in the prolongation of life. If one adds them together as an intermediate group between the untreated or practically untreated patients of group 1 and the well treated patients of group 4, the figures are as follows: of 16 patients, 5 are still living and 11 are dead, a mortality of 68 per cent. The average duration of

31 Lucke, B., and Rea, M. H. Studies on Aneurysm. I. General Statistical Data, J. A. M. A. 77:935 (Sept. 17) 1921.

life, dating from the onset of symptoms, is, in the 5 living patients, 72 months, in the 11 dead patients, 44 months

EFFECT OF TREATMENT ON PROLONGATION OF LIFE IN PATIENTS
WITH AORTIC REGURGITATION

An identical presentation of data for 112 patients with aortic regurgitation appears in table 13. Again contrast the untreated patients of group 1 with the well treated patients of group 4. Of the 57 patients in group 1, 5 are living and 52 are dead, a mortality of 91 per cent. The average duration of life for the whole group, dating from the onset of symptoms, was 30 months. For the 52 dead patients, death followed the appearance of symptoms in an average of 27 months. Fourteen died within the first year, 15 in the second year, 7 in the third, 5 in the fourth and 7 in the fifth. Three lived for more than 5 years after symptoms first developed. The extremes of duration of life were 1 month and 78 months, respectively. In the 5 patients in this group still alive, the duration of life from the onset of symptoms until the present has been 36, 54, 66, 72 and 134 months, respectively, an average of 72 months. Here again yawns the pitfall of misinterpretation of the value of therapy on the basis of individual instances. These 5 patients, all untreated, have lived fairly comfortably for a time far greater than the average.

Now compare these data and the mortality of 91 per cent with the corresponding data and mortality of group 4. Of these 25 well treated patients, 21 are still living and 4 are dead. The mortality is 16 per cent. The 4 dead patients died in an average of 28 months after symptoms appeared. The 21 living patients have lived for an average period of 71 months (extremes, 24 and 159 months). The living patients have so far lived no longer, on the average, than those still living in group I, but there are far more of them (84 per cent as compared with 9 per cent of the respective groups).

The duration of life in untreated patients with aortic regurgitation is longer than in those with aneurysm of the aorta—27 as compared with 16 months, and the average prolongation of life obtainable in well treated patients with the former condition is distinctly less. It is also worth noting, though the number of cases of both types is too small for one to be sure, that apparently a little antisyphilitic treatment has a distinctly harmful effect on patients with aortic regurgitation, as compared with its apparently beneficial effect on those with aneurysm, in this series, in the patients with aortic insufficiency in group 2 the average duration of life was actually less than that in the group in which no treatment was given. This is probably a reflection of the relationship of congestive heart failure to the ultimate outcome, a point presently discussed in detail.

EFFECT OF TREATMENT ON PROLONGATION OF LIFE IN PATIENTS WITH CARDIOVASCULAR SYPHILIS

When these data were incompletely presented at the meeting of the American Heart Association, an eminent physician commented in discussion³² on the possibility that this and other studies reported were not statistically significant because the number of observations was so small and the probable error so great. It hardly needs emphasis that it is difficult for any single group of observers to collect a large series of adequately studied and followed cases of cardiovascular syphilis. So far as we are aware, the material of the present paper is the largest available. It has occurred to us that statistical accuracy might be better

TABLE 14—*Effect of Treatment on Prolongation of Life in Whole Group of Patients with Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Number of Patients in Group	Number Living	Number Dead	Average Duration of Life Until Death or Last Observation, Dating from	
				Onset of Symptoms	Start of Treatment
Group 1 Patients with no treatment or very little	79	7	72	27 mo	21 mo
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	26	6	20	33 mo	26 mo
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	20	13	7	46 mo	39 mo
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	40	30	10	68 mo	57 mo

served if we grouped together as presenting cardiovascular syphilis all of our patients with aortic aneurysm and aortic regurgitation. The two conditions have many things in common, and this use of the material, by providing larger numbers in each of our treatment groups, decreases the probable statistical error. This has accordingly been done in table 14. Since the two preceding tables have been analyzed in the text, the data of table 14 are allowed to stand without detailed explanation.

The question as to whether these figures actually are statistically significant was submitted to L J Usilton, statistician of the United States Public Health Service. She replied³³ that this could be determined if we grouped together as presenting cardiovascular syphilis all of our patients with aortic aneurysm and aortic regurgitation. The two conditions have many things in common, and this use of the material, by providing larger numbers in each of our treatment groups, decreases the probable statistical error. This has accordingly been done in table 14. Since the two preceding tables have been analyzed in the text, the data of table 14 are allowed to stand without detailed explanation.

³² Emerson, Haven, in discussion of paper by Wife, U J. Am Heart J 6 161, 1930

³³ Usilton, L J. Personal communication

mined only from a knowledge of the total number of cases in each treatment group, from which the reported material was drawn. When this was investigated, it was found, for example, that there were 128 patients with cardiovascular syphilis in treatment group 1, of whom we had been able to trace only 79 until death or the present time, while of a total of 45 cases in treatment group 4, we had succeeded in tracing 40. To paraphrase Usilton's comment, "If one considers that the end-result is known in 89 per cent of group 4 and in only 61 per cent of group 1, the probabilities are that adequate treatment prolongs the life of the individual with cardiovascular syphilis. Further, the pro-

TABLE 15—*Effect of Treatment on Prolongation of Life in Patients with Cardiovascular Syphilis, Computed on Living and Dead Patients Separately*

Treatment Group	Number of Patients in Group	Number Living	Average Duration of Life to Last Observation, Dating from		Number Dead	Average Duration of Life to Death, Dating from	
			Onset of Symptoms	Start of Treatment		Onset of Symptoms	Start of Treatment
Group 1 Patients with no treatment or very little	79	7	68 mo	67 mo	72	23 mo	16 mo
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	26	6	62 mo	52 mo	20	25 mo	19 mo
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	20	13	45 mo	36 mo	7	49 mo	44 mo
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	40	30	76 mo	66 mo	10	45 mo	30 mo

longation of life is placed at a minimum in the 68 months shown for group 4, because the termination of life has not yet occurred in 30 of the 40 persons in this group, whereas only 7 of 79 patients are still living in group 1, and yet the average life period from the onset of symptoms is 27 months." In other words, the average duration of life for patients in group 1 cannot be greatly affected no matter how long the surviving 7 patients may live, while the longer the surviving 30 patients of group 4 continue to live, the greater the increase of the average duration of life in this group. There can be no doubt, we believe, that our data are statistically significant.

An attempt to solve this difficulty in another way is shown in table 15. Here we show the duration of life for living and for dead patients separately. With the duration of life measured from the onset

of symptoms, it appears that in the living patients there is little or no significant increase in the duration of life corresponding to whether the patients were untreated or well treated. The probable explanation for this is that the period of time covered by the study is roughly the past ten years, and that not enough time has elapsed to bring out a difference even in the two extreme groups. So far as living patients are concerned, we must at present stand on the fact that the percentage probability of survival for the period of observation is in direct proportion to the amount of treatment given, i. e., for group 1, 8 per cent, group 2, 23 per cent, group 3, 65 per cent, group 4, 75 per cent.

If one turns to the patients now dead, however, it seems fairly definite that, even though the outcome was death, the duration of life was approximately doubled by good treatment as compared with little or none.

RELATIONSHIP OF DURATION OF SYMPTOMS AND OF CONGESTIVE HEART FAILURE TO THE OUTCOME OF TREATMENT IN CARDIOVASCULAR SYPHILIS

An obvious objection that may be leveled at the conclusions that we have so far drawn is that the material in the various treatment groups is not comparable, that the more seriously ill patients are those who died, and that the survivals represent patients with less serious or less rapidly progressive lesions. We have attempted to view our material critically from this standpoint. Since we avoid placing undue emphasis on the individual case, we have taken as our criteria of relative seriousness, first, the average duration of symptoms in the various treatment groups, second, the number of patients who were symptom-free before treatment was begun, and third, the number who had and the number who did not have congestive heart failure before or after treatment. These data appear in table 16. Patients with aneurysm and those with aortic regurgitation are grouped as patients with cardiovascular syphilis in this and most of the subsequent tables, since there are no significant differences between the two groups.

The term "duration of symptoms" refers here, as elsewhere in this paper, to the length of time during which the patient has suffered from one or more of the commonly accepted symptoms of cardiovascular syphilis. It will be noted that there are no important differences in the various treatment groups. Certainly, it is not true that the well treated patients, with only 25 per cent dead, had had symptoms for a much shorter period of time than the untreated group, with 89 per cent dead. Indeed, the reverse appears to be the case.

It might *a priori* be supposed that patients who had never had any symptoms, the existence of the lesion being accidentally discovered at routine examination, were particularly suitable subjects for treatment.

That this is usually, but not always, true is indicated by the fact that 11 of 20 such patients are living, while 9 are dead. One of these died of sarcoma, another of miliary tuberculosis, and the remaining 7 of cardiovascular syphilis. Among the 11 surviving patients originally symptom-free, 7 are still perfectly well and working, no symptoms having developed. In the remaining 4, symptoms have appeared in spite of treatment, 2 of these are, however, still able to do light work, and 2 are incapacitated by the progress of their disease.

TABLE 16—*Relationship of Duration of Symptoms and of Cardiac Failure to Outcome of Treatment in Patients with Cardiovascular Syphilis*

Treatment Group	Total Number of Patients	Average Duration of Symptoms Before Treatment	Number of Patients Symptomless Before Treatment	Number Who Did Not Have Cardiac Failure		Number Who Had Cardiac Failure		No on Whom No Data Was Obtained as to Cardiac Failure	
				Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Group 1 Patients with no treatment or very little									
Living	7	2 mo		6	2	1	2		3
Dead	72	9 mo	5	30	10	41	29	1	33
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)									
Living	6	14 mo	2	6	2		4		
Dead	20	7 mo	2	10	3	9	12	1	5
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)									
Living	13	13 mo	3	9	6	4	5		2
Dead	7	6 mo	1	5	3	2	2		2
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal									
Living	30	12 mo	6	23	22	7	5		3
Dead	10	17 mo	1	7	5	3	5		
Total living	56		11	44	32	12	16		8
Total dead	109		9	52	21	55	48	2	40

The occurrence of congestive heart failure before the institution of treatment is of unfavorable prognostic import. In this series, it was less a feature in patients with aneurysm, only 27 per cent of whom suffered from decompensation or had previously suffered from congestive failure at the time of admission, than in those with aortic regurgitation, 46 per cent of whom were or had been so affected. Taking the group as a whole, 21 per cent of those still living had had heart failure before treatment, while it had occurred in 51 per cent of those now dead. Of 67 patients who had, or had had cardiac failure when treatment was

started, 12 are now living and 55 are dead, a mortality of 81 per cent. The average duration of life for the 12 survivors is 54 months, for the 55 who died, 24 months. Of the 96 who had not lost compensation before treatment, the corresponding figures are living 44, average duration of life 69 months, dead 52, average duration of life 30 months, mortality 56 per cent. It appears, therefore, that the appearance of cardiac failure before treatment is started shortens life, on the average, by from 6 to 15 months. These data are shown in more detail for the various treatment groups in table 17. That congestive failure is not

TABLE 17—*Relationship of Congestive Heart Failure to Outcome of Treatment in Patients with Cardiovascular Syphilis*

Treatment Group	Total Number of Patients in Sub group	Number of Patients Living	Average Duration of Symptoms, Onset to Present	Number of Patients Dead	Average Duration of Symptoms, Onset to Death
Group 1 Patients with no treatment or very little					
Subgroup A*	41	1	66 mo	40	23 mo
Subgroup B†	36	6	68 mo	30	26 mo
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)					
Subgroup A	9			9	17 mo
Subgroup B	16	6	66 mo	10	31 mo
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)					
Subgroup A	7	5	53 mo	2	27 mo
Subgroup B	14	9	40 mo	5	57 mo
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal					
Subgroup A	9	6	52 mo	3	63 mo
Subgroup B	30	23	81 mo	7	31 mo

* Patients in whom congestive heart failure was present before treatment

† Patients in whom congestive heart failure was not present before treatment

necessarily a barrier to a successful outcome of treatment is indicated by the fact that 12 of the surviving patients, 11 of whom were subsequently treated, had had decompensation before treatment was begun. In several of these patients, heart failure was extreme and recovery of compensation despaired of.

We attach less importance to the occurrence of attacks of congestive heart failure during or after treatment, though this was observed in only 33 per cent of those still living as contrasted with 69 per cent of those now dead (percentages calculated on total number of cases in which information was available). To some extent, at least, congestive heart failure occurring before treatment is started predisposes to subsequent similar attacks, as may be seen from the data of table 18. Here infor-

mation is provided as to the occurrence of cardiac failure during or after treatment in 46 patients who had experienced cardiac failure before treatment and in 70 who had not. The incidence of cardiac failure after treatment is 82 per cent in the former and only 40 per cent in the latter group. It is also apparent, however, that while congestive heart failure occurring during or after treatment is a serious complication, it need

TABLE 18—*Relationship of Congestive Heart Failure Before Treatment to Heart Failure Occurring During or After Treatment*

Treatment Group	Total Number of Patients in Subgroup	Number Living	Number Who Had Cardiac Failure During or After Treatment	Number on Whom No Data as to This Was Obtained	Number Dead	Number Who Had Cardiac Failure During or After Treatment	Number on Whom No Data as to This Was Obtained
Group 1 Patients with no treatment or very little							
Subgroup A*	41	1		1	40	22	15
Subgroup B†	36	6	2	2	30	9	14
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)							
Subgroup A	9				9	6	3
Subgroup B	16	6	4	2	10	5	2
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)							
Subgroup A	7	5	5		2	2	
Subgroup B	14	9	1	6	5	1	3
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal							
Subgroup A	9	6	1	4	3	2	1
Subgroup B	30	23	4	17	7	2	1
Total							
Subgroup A	66	12	6	4	54	32	18
Subgroup B	96	44	11	27	52	17	20

* Patients in whom congestive heart failure was present before treatment

† Patients in whom congestive heart failure was not present before treatment

not prove to be more of a hindrance to a successful outcome than cardiac failure before treatment. Seventeen patients still living have had one or more attacks of heart failure since treatment was started, and six of these also had decompensation before any treatment was given.

In many instances, especially among Negro males, repeated attacks of cardiac failure occurred after treatment had started because of economic exigencies beyond our control or that of the patient. While we have made every effort to assist patients in obtaining light work, we

have not always been able to do so. The necessity of earning a bare living led many patients to return to former jobs even if they involved heavy physical labor. The cardiac reserve, estimated to be adequate to maintain the circulation during decreased activity, was unequal to the strain of stevedoing, hod-carrying, etc. Were we able to apply the ideal of restricted activity to all cases, the incidence of failure following the institution of treatment would be much lower. Indeed, considering the fact that our patients were drawn almost entirely from the laboring class, that the majority were Negroes, who are notoriously uncooperative

TABLE 19—*Present Status of Living Patients Treated for Aneurysm and Aortic Regurgitation*

Treatment Group	Cardiovascular Condition	Number of Patients in Group Who Are Living	Number of These of Status Indicated		
			Have No Symptoms and Are Working	Have Persistent Symptoms but Are Able to Work	Have Persistent Symptoms and Are Incapacitated
Group 1 Patients with no treatment or very little	Aneurysm	2		1	1
	Aortic regurgitation	5	3	2	
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	Aneurysm	2			2
	Aortic regurgitation	4	1	2	1
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	Aneurysm	3	2	1	
	Aortic regurgitation	10	2	5	3
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	Aneurysm	9	3	6	
	Aortic regurgitation	21	10	9	2
Total		56	21	26	9

patients, and that treatment was carried out under the relatively inadequate conditions of an outpatient ambulant clinic, we feel that our results represent the minimum of benefit obtainable, rather than the possible maximum.

PRESENT STATUS OF LIVING PATIENTS WITH CARDIOVASCULAR SYPHILIS

Mere prolongation of life past the usual period of time would be of relatively small value to the patient if he remained completely incapacitated. It is therefore important to determine to what extent surviving patients are comfortable, free from incapacitating symptoms and able to work. Figures bearing on these points are presented in table 19. If

the group is taken as a whole it will be seen that 21 of the 56 survivors are symptom-free and able to work "Symptom-free," in these patients means almost exactly what it says. In most instances, of course, violent physical exercise results in a moderate amount of exertional dyspnea, but aside from this these patients are able to perform the ordinary tasks of their daily life without dyspnea, exertional or paroxysmal, and without pain or discomfort. Some of them, despite advice to the contrary, are still working at jobs involving heavy physical labor. Seven of these 21 patients are those who were symptom-free before treatment was started. The remaining 14, however, all had definite, sometimes incapacitating, symptoms before treatment. Included among the symptom-free group are 5 patients with aneurysm and 16 with aortic regurgitation.

Twenty-six patients, 9 with aneurysm and 17 with aortic regurgitation, are able to work regularly at some occupation involving little or no physical effort, such as preaching, boot-legging, etc., even though some symptoms persist. Most of these persons are distinctly better than before treatment was started, and the persisting symptoms are often very mild. It is important to note that 13 of the 21 symptom-free patients and 15 of the 26 who are able to work in spite of some remaining symptoms have been well treated (group 4) according to the scheme outlined in this paper.

Only 9 of the 56 surviving patients (3 with aneurysm and 6 with aortic insufficiency) are incapacitated and unable to do any work.

SYMPTOMATIC RELIEF FOLLOWING TREATMENT IN CARDIOVASCULAR SYPHILIS

Any one who has treated large numbers of patients with cardiovascular syphilis is struck by the prompt symptomatic relief that follows the improvement in the cardiac embarrassment and the institution of anti-syphilitic treatment. It may be in part due, as Wile³⁰ insisted, to the general sense of well being that pervades any patient with late syphilis shortly after the institution of treatment, even though he may not have been feeling ill before. There is more than this, however, relief extends also to symptoms directly due to the cardiovascular lesion, especially paroxysmal and exertional dyspnea and pain. It is often so complete after a short time that the ignorant patient regards himself as cured, abandons further treatment and fails to return until the reappearance of distressing symptoms or a sudden cardiac break, occurring weeks or months later, forces him to seek relief anew. Without attempting the analysis of individual symptoms, details of which may be found in the paper by Hines and Carr,³⁴ we present the gross data as to symptomatic

34 Hines and Carr (footnote 28, fourth reference)

relief in table 20 We have excluded from consideration all patients who were symptom-free before treatment started, all those who received no treatment and those on whom adequate information was lacking Included in treatment group 1 are patients who received, for example, as little treatment as one or two doses of arsphenamine, three or four injections of bismuth, or injections with mercury for a month or less Even this infinitesimal amount of treatment brought about great symptomatic improvement in 3 of 11 patients with aneurysm and 6 of 20 with aortic regurgitation It may easily be objected, and is perhaps true, that in these cases the relief was due not so much to antisyphilitic

TABLE 20—*Symptomatic Relief from Antisyphilitic Treatment in Cardiovascular Syphilis*

Treatment Group	Patients with Aneurysm*			Patients with Aortic Regurgitation*		
	Total Number	Number Who Obtained Symptomatic Relief	Number Who Obtained No Relief	Total Number	Number Who Obtained Symptomatic Relief	Number Who Obtained No Relief
Group 1 Patients with no treatment or very little	11	3	8	26	3	20
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	7	4	3	13	2	11
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	5	4	1	12	10	2
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	11	10	1	20	19	1
Total	34	21	13	71	37	33

* Excluding all who were not treated, those who were symptomless before treatment, and those in whom reliable data are lacking

treatment as to the adjuvant medical measures of rest, digitalization, etc It will be seen, however, that the probability of symptomatic relief is in direct proportion to the amount of treatment given Of adequately treated patients (group 4), all except 1 of 11 patients with aneurysm and 1 of 20 with aortic regurgitation were markedly improved by treatment While improvement is often dramatically prompt, as we have noted, it is sometimes discouragingly slow, and persistence and encouragement over a period of many months may be necessary In some patients, discontinuance of antisyphilitic treatment is followed by a prompt recrudescence of symptoms, as illustrated by a patient with abdominal aneurysm who was free from pain as long as he was under treatment, but whose pain recurred after each lapse of a few weeks

These data, as well as those given in table 19 as to the present status of living patients, constitute as forceful an argument for the adequate antisyphilitic treatment of cardiovascular syphilis as do the figures given for prolongation of life

ALTERATION OF PHYSICAL SIGNS BY TREATMENT

Stokes³⁵ and Brooks,²⁹ among other writers, emphasized not only symptomatic improvement resulting from treatment, but also improvement or alteration in physical signs. In apparently uncomplicated aortitis, for example, the institution of treatment may be shortly followed by the appearance of a diastolic murmur, not previously heard, an aneurysmal sac may pulsate more widely after than before treatment, owing to the resolution of the inflammatory tissue in syphilitic mediastinitis or peri-aortitis, a faint diastolic murmur may become much louder. This paradoxical increase in physical signs is not so bad as it seems. As Stokes put it, "The patient has exchanged a progressive disability for an arrested and static one." These phenomena are sometimes of great value as a therapeutic test in suspected but Wassermann-negative cardiovascular syphilis. On the other hand, cardiac murmurs may completely disappear, aortic widening as measured by teleroentgenography may decrease, and rarely a definite sacculation of the aorta may vanish. Stokes³⁶ reported one such "disappearing aneurysm," and we have seen another, which will be separately reported.³⁷ We have made no attempt at tabulation of changes in physical signs during or after treatment in our material, though we agree with Stokes and Brooks that such changes infrequently occur.

INFLUENCE OF TREATMENT IN CARDIOVASCULAR SYPHILIS ON ABILITY TO WORK

The question of the utility of treatment may be approached from still another angle, namely, ability to work before and after treatment. This information is gathered in table 21. The figures speak for themselves. Let us compare the percentage probability of various outcomes in inadequately treated (groups 1 and 2) as compared with relatively adequately treated (groups 3 and 4) patients. Of 69 patients in groups 1 and 2, 62 per cent were unable to work either before or after the institution of treatment, 21 per cent were unable to work before, but could work afterward, 8 per cent, able to work before, were unable afterward, and 6 per cent were able to work both before and after treatment. Con-

35 Stokes (footnote 17, p. 832)

36 Stokes (footnote 17, p. 886)

37 Moore, J. E., Dangle, J. H., and Reisinger, J. C. Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm. Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients, *Arch. Int. Med.* **49**: 752 (May) 1932.

trast this with the corresponding figures for the 49 patients in groups 3 and 4. Only 16 per cent were unable to work before or after treatment, 39 per cent were so improved by treatment that, unable to work before, they could work afterward, none of those able to work before grew so much worse under treatment as to be unable to work afterward, while 44 per cent, able to work before, were maintained in a sufficiently good state of health as to be able to continue afterward.

TABLE 21—*Influence of Treatment on Ability to Work in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Number of Patients with Data Available	Number Unable to Work Before or After Treatment	Number Unable to Work Before, but Able After Treatment	Number Able to Work Before, but Unable After Treatment	Number Able to Work Before and After Treatment
Group 1 Patients with no treatment or very little	52	37	8	5	2
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	17	6	7	1	3
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	16	3	7		6
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four courses of a heavy metal	33	5	12		16

TABLE 22—*Average Period of Incapacity After Varying Amounts of Treatment in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Number of Patients with Data Available	Number Never Incapacitated Until Final Illness or Last Observation	Average Period of Incapacity
Group 1 Patients with no treatment or very little	46	2	15 mo
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	15	2	14 mo
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	19	6	9 mo
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	35	16	10 mo

AVERAGE PERIOD OF INCAPACITY AFTER VARYING AMOUNTS OF TREATMENT IN CARDIOVASCULAR SYPHILIS

It may seem like piling Ossa on Pelion to adduce still further evidence that the antisypilitic treatment for cardiovascular syphilis is of value. The prevailing skepticism of many physicians makes it of the utmost importance to consider the question from all possible angles. In table

22, we present data relative to the total period of incapacity of the patients in our various treatment groups. Comparing again untreated or inadequately treated patients (groups 1 and 2) with those receiving relatively adequate treatment (groups 3 and 4), we point out that only 6 per cent of the 61 patients of the former, as compared with 40 per cent of the 54 patients of the latter, classification, were never incapacitated until the date of the last observation or the onset of the final illness. This is, of course, a direct reflection of the incidence of congestive heart failure before and after treatment, a factor already analyzed in tables 16, 17 and 18. The average period of incapacity for the patients of groups 1 and 2 was between fourteen and fifteen months, that for the patients of groups 3 and 4 was between nine and ten months. When

TABLE 23—*Cause of Death in Aneurysm*

Treatment Group	Number Dead	Number Who Died of Cardiovascular Syphilis		Number Who Died, Cause Unknown	Number Who Died from Other Cause
		Death Probably or Certainly Gradual	Sudden Death		
Group 1 Patients with no treatment or very little	20	8	8	3	1 (pulmonary tuberculosis)
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal from (1½ to 4 months)	8	3	1	2	2 (1 pulmonary tuberculosis, 1 chronic nephritis)
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	3	3			
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	6	3	1		2 (1 miliary tuberculosis, 1 carcinoma)
Total	37	17	10	5	5

one considers that the well treated patients have been under observation for periods of time averaging from twice to three times as long as those untreated or poorly treated, these figures take on added significance.

CAUSE OF DEATH IN TREATED PATIENTS WITH ANEURYSM AND AORTIC REGURGITATION

Our information concerning the causes of death in the patients of this series was gathered from personal observation of patients who died while under our supervision, from the records of other hospitals, from the data given on death certificates signed by outside physicians, and from descriptions of patients' last illnesses supplied by relatives or by friends. The inclusion of the last two sources of information, and the absence of a necropsy in most instances, introduce an unavoidable inaccuracy into our statements. However, we present the data for what they

are worth in tables 23 and 24 Fifty-seven patients, of whom 17 had aortic aneurysm and 40 aortic regurgitation, died from progressive cardiac failure, presumably due, of course, to cardiovascular syphilis Ten patients with aneurysm, or 27 per cent of those dead, and 18 with aortic regurgitation, or 25 per cent of those dead, died suddenly, that is, the patients, previously in their usual state of health, dropped dead or were found dead in bed Rupture of the aneurysm was the usual cause of sudden death in the patients with this condition The precise cause of

TABLE 24—Cause of Death in Aortic Regurgitation

Treatment Group	Number Dead	Number Who Died of Cardiovascular Syphilis		Number Who Died, Cause Unknown	Number Who Died from Other Cause
		Death Probably or Certainly Gradual	Sudden Death		
Group 1 Patients with no treatment or very little	52	29	13	5	5 (1 chronic nephritis, 1 carcinoma, 1 acute nephritis, 1 pulmonary tuberculosis, 1 tuberculous meningitis)
Group 2 Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	12	8	2	1	1 (pulmonary tuberculosis)
Group 3 Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	4	2	1		1 (sarcoma)
Group 4 Patients treated for more than 1 year two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	4	1	2		1 (lobar pneumonia)
Total	72	40	18	6	8

sudden death in patients with aortic regurgitation is not clear, in spite of numerous pathologic studies by Warthin,³⁸ Martland³⁹ and others, it is certainly not always, nor apparently even often, due to sudden coronary occlusion, and it is difficult to be satisfied with Warthin's explanation that it is due to cardiac insufficiency and dilatation resulting from diffuse interstitial myocarditis of slight degree, leading eventually to fibrosis

38 Warthin, A S The Role of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis, and of Sudden Cardiac Death, *Am Heart J* 6 163, 1930

39 Martland, H S Syphilis of the Aorta and Heart, *Am Heart J* 6 1, 1930

Eleven patients were reported by relatives or by friends to have died, but the information supplied was too meager for us to assign any definite cause. Presumably most of them died from cardiovascular syphilis.

Thirteen patients, 5 with aneurysm and 8 with aortic regurgitation died from illnesses unrelated to cardiovascular syphilis. The causes of death are given in the tables. Four of these patients (the two with aneurysm who died of carcinoma and miliary tuberculosis, respectively, and the two with aortic regurgitation who died of sarcoma and lobar pneumonia, respectively, in each instance after adequate treatment for syphilis) were doing exceptionally well from the standpoint of cardiovascular syphilis at the time of death.

USE OF ARSENICAL DRUGS IN CARDIOVASCULAR SYPHILIS

We have repeatedly stressed in this paper and elsewhere that one aim of treatment in cardiovascular syphilis is the absolute avoidance of

TABLE 25—*Use of Arsenical Drugs in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Type of Arsenical Drug Administered	Number of Patients Receiving Drug*	Number Who Gave Serious Reactions
Neoarsphenamine	60	3
Arsphenamine	30	4
Silver arsphenamine	14	0
Tryparsamide	14	1
Sulpharsphenamine	1	0
Bismarsen	1	0

* The total number of patients treated with some arsenical product was 92; the total number of patients receiving bismuth or mercury (and potassium iodide) was only 50.

reactions to treatment. Even such otherwise unimportant reactions as slight nausea and vomiting throw an undue strain on an overburdened heart which must be eliminated if possible. Therapeutic shock (the Jarisch-Herxheimer reaction) and the therapeutic paradox are irremediable disasters. The loss of many of our older records (prior to 1920) through the inadequate system of cross-indexing prevalent at the time prevents us from including here a report on the frequency of sudden death following the use of average therapeutic doses of old arsphenamine. We have observed at least four instances of such deaths, not included in this series.

We have thought it profitable, however, to inquire into the various arsenical drugs given our patients and the incidence of serious or alarming reactions following their use. This information is summarized in table 25. Twenty-three of the 165 patients in this series received no treatment of any kind and are eliminated from consideration in the table. Fifty were treated exclusively with a heavy metal (bismuth or mercury)

and the iodides This is a reflection of two factors, first, that in many patients with preceding heart failure and a low cardiac reserve the use of arsenical drugs was thought to be contraindicated, second, that many patients were so much improved symptomatically after a single course of a heavy metal that they failed to return for further treatment

Ninety-two patients were treated with one or more of the arsenical drugs listed The majority received neoarsphenamine in small dosage (from 0.1 to 0.45 Gm, rarely more than 0.3 Gm) In 3 of 60 patients so treated, the use of this drug was followed by reactions severe enough to preclude its further employment A shower of ventricular extrasystoles was precipitated by each injection in one patient, while, in the other two, each attempt at this type of treatment was followed by fever, nausea and vomiting and extreme malaise lasting over a period of several days There were no instances of sudden death following the use of neoarsphenamine

Thirty patients received old arsphenamine (606) in a dosage usually not exceeding 0.1 Gm Of these, 2 died suddenly within twenty-four hours following a treatment In one, death resulted from circulatory collapse on the treatment table, probably to be ascribed to ventricular fibrillation resulting from the direct toxic action of the drug on a damaged myocardium, in one, sudden death resulted from a ruptured aneurysm about eighteen hours after the first injection of the drug, which in this case had not been preceded by any preparatory treatment This death was almost certainly a Jarisch-Herxheimer effect—therapeutic shock In another patient, circulatory collapse occurred on the table during treatment, but the patient recovered after forty-eight anxious hours The fourth serious reaction occurred in one of the patients who reacted badly after neoarsphenamine, and was identical with the after-effects of that drug

In 14 patients treated with silver arsphenamine, 1 with sulpharsphenamine and 1 with bismarsen, there were no serious reactions The number of patients given silver arsphenamine is too small for us to express an opinion as to its therapeutic efficacy We have the impression that it may be profitable to attempt its use in small doses (from 0.05 to 0.1 Gm) in patients in whom mild reactions developed after the use of neoarsphenamine, and that it may be equally efficacious from the therapeutic standpoint Sulpharsphenamine has been dropped from our therapeutic armamentarium not because of any special deleterious effect in cardiovascular syphilis, but because of the generally high incidence of dermatitis and blood dyscrasias following its use We are employing bismarsen with increasing frequency in cardiovascular syphilis, but none of the patients treated with it have as yet been followed long enough to justify their inclusion in this series

Tryparsamide has been employed in 14 patients, practically all of whom had complicating neurosyphilis. One patient died of a ruptured aneurysm twenty-four hours after the first dose (probable therapeutic shock). Aside from this case, the use of tryparsamide in average therapeutic dosage (3 Gm.) was not attended by any deleterious after-effect on the cardiovascular apparatus. On the other hand, we have seen nothing to indicate that it has any therapeutic value in cardiovascular syphilis, and believe that its use should be limited to those patients in whom involvement of the central nervous system is a complicating feature. Even here it should not be employed until thorough preparatory treatment has been given.

Our experience demonstrates, we think, that therapeutic shock can be almost entirely eliminated as an important factor in the treatment of patients with cardiovascular syphilis by long and thorough preparatory treatment with bismuth or mercury and the iodides, and by an appropriate small dosage of the arsphenamine employed. The arsenical product of choice in our experience is neoarsphenamine, with bismarsen second and silver arsphenamine third. Old arsphenamine should never be used in any dosage in a patient with cardiovascular syphilis (except uncomplicated aortitis, of which more will be said in a subsequent communication).

We can offer no statistical information as to the incidence of the therapeutic paradox. In 66 patients, congestive heart failure developed after treatment had begun, but the factors leading to this difficulty are so numerous and complex as to defy further analysis than we have already attempted. Individual cases might be cited to show that the therapeutic paradox is an important consideration. It can be largely avoided, we think, only by proper attention to adequate preparatory treatment, a correct estimate of the cardiac reserve, clinical acumen in selecting the proper time, drug and dosage for arsenical treatment, and the intelligent use of digitalis, rest and restriction of activity.

EFFECT OF ANTISYPHILITIC TREATMENT ON THE WASSERMANN REACTION OF THE BLOOD IN CARDIOVASCULAR SYPHILIS

The least important effect of treatment in cardiovascular syphilis is that on the Wassermann reaction of the blood. As has been repeatedly pointed out, patients with this type of syphilitic lesion are prone to have a persistently positive Wassermann reaction of the blood in spite of treatment. Information on this point is summarized in table 26. The important point is that 57 per cent of the 33 patients in treatment group 4 had a fixed positive Wassermann reaction after a great deal of treatment. We feel that, for all practical purposes, the response of this reaction of the blood to treatment may be completely disregarded.

in cardiovascular syphilis. It is most unwise to base the discontinuance of treatment on the condition of obtaining a negative Wassermann reaction. This may never be accomplished, on the one hand, and on the other, if treatment is stopped when the reaction becomes negative or remains so for any arbitrary period of time, the patient may be deprived of the treatment which he needs to keep his lesion quiescent. Clinical and pathologic progression may and often does occur in the presence of a negative Wassermann reaction of the blood. It is important to reassure the patient of the relative lack of significance of a persistently positive reaction, since otherwise he may become discouraged by what seems to him the apparent inefficacy of the treatment.

The aim of treatment in cardiovascular syphilis is to maintain the patient in relatively good health over as long a period of time as possible. Radical cure of the syphilitic infection is of course out of the question.

TABLE 26—*Effect of Antisyphilitic Treatment on the Wassermann Reaction of the Blood in Patients with Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Total Number of Patients	Number the Wassermann Reaction of Whose Blood		
		Remained Positive	Was Reduced	Was Reversed
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	19	12	2	5
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	19	15	1	3
Group 4. Patients treated for more than 1 year—two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	35	19		14

SUMMARY AND CONCLUSIONS

1 We present a general consideration of the subject of the treatment of cardiovascular syphilis, based on 53 patients with aortic aneurysm and 112 with aortic regurgitation. At the same time our material permits some conclusions bearing on important questions of the incidence of cardiovascular syphilis.

2 An earlier study of the outcome of treatment in early syphilis in our clinic revealed that cardiovascular syphilis developed among these treated patients in inverse ratio to the amount of treatment given early in the infection. Not one of 117 patients with early syphilis who received three or more courses of arsphenamine, and treatment with mercury during periods between the courses, presented any evidence of cardiovascular involvement during the period of observation, while 24 of

285 patients who had received less than this amount of treatment were observed to acquire syphilitic aortitis, aneurysm or aortic regurgitation. Adequate treatment for early syphilis almost certainly protects the majority of patients so treated against subsequent cardiovascular syphilis.

3 Of 6,420 patients from our own clinic with various forms of late syphilis, 10 per cent had cardiovascular syphilis. Of the total number, 27 per cent had aortic regurgitation and 12 per cent aortic aneurysm. These were the clinical diagnoses on admission to the hospital.

4 Cardiovascular syphilis is twice as common in males as in females and about twice as common in Negro as in white patients.

5 Pathologic studies carried out by various investigators indicate that from 70 to 90 per cent of all patients with late syphilis show postmortem evidence of syphilis of the aorta.

6 The majority of cases of aneurysm and aortic regurgitation occur in the fifth decade of life. White patients appear to be affected later in life than Negroes, and males later than females.

7 About one half of all patients with cardiovascular syphilis can give no history of infection with syphilis. Symptomless infection must be a fairly frequent occurrence. The average interval of time between infection and the development of cardiovascular symptoms is about twenty years.

8 In 20 of our 165 patients, the aneurysm or the aortic regurgitation had caused no symptoms, and was accidentally discovered during routine physical examination. The onset of symptoms was usually abrupt, but sometimes was slow and insidious.

9 All except 13 of the 165 patients in this series had been subjected to the strain of hard physical labor.

10 The most frequent association with other lesions of syphilis was that with syphilis of the central nervous system (especially tabes dorsalis), which occurred in from 17 to 18 per cent of our patients.

11 An additional 17 per cent of patients with cardiovascular syphilis, but without clinical evidence of neurosyphilis, had abnormal spinal fluids. The actual incidence of complicating neurosyphilis was thus about 35 per cent.

12 Positive Wassermann reactions of the blood were obtained for 98 per cent of our patients with aneurysm, and 96 per cent of those with aortic regurgitation.

13 The association of cardiovascular syphilis and neurosyphilis as a complicating factor in treatment is discussed.

14 One hundred and forty-seven (89 per cent) of our patients had never received any treatment for syphilis before the development of cardiovascular syphilis. Of the remainder, not one had received ade-

quate treatment for early syphilis. Only 4 of the 165 had received arsphenamine at the time of early syphilis, and none of these got more than three injections.

15 These data, with those given in the second paragraph of this summary, constitute a powerful argument for the adequate treatment of early syphilis. They also indicate that modern antisyphilitic treatment is probably not responsible for the apparent increase in the incidence of syphilitic aortitis.

16 The literature on the treatment of cardiovascular syphilis is briefly reviewed.

17 The evolution of the method of treatment now in use by us and, subject to minor modifications, by many other investigators, is outlined. Especially stress is laid on sudden death during or immediately following the administration of arsphenamine to patients with syphilitic heart disease, presumably due to ventricular fibrillation, on sudden death from twenty-four to forty-eight hours following an injection, due to therapeutic shock (the Jaisch-Herxheimer reaction), and on the therapeutic paradox.

18 The measures taken to avoid these reactions have resulted in the adoption of a method of treatment which is described in detail. This method includes adequate general medical care and the cautious use of mercury, bismuth, the iodides, neoarsphenamine and bismarsen in small doses. All reactions to treatment are meticulously avoided, and treatment is prolonged over a period of years.

19 Using this method of treatment and subdividing our material into four groups, on the basis of the amount of treatment given, we have shown that in 22 patients with aortic aneurysm, who received little or no treatment, the mortality during the period of observation was 90 per cent, and that the average duration of life from the onset of symptoms to deaths or, in living patients, to the last observation, was 19 months. In 15 well treated patients with aortic aneurysm, the mortality was 40 per cent, and the average duration of life 75 months.

20 The mortality in 57 patients with aortic regurgitation who received little or no treatment was 91 per cent, and the average duration of life 30 months. In 25 well treated patients, the mortality was 16 per cent, and the average duration of life 71 months.

21 It is mathematically demonstrable that these data are probably statistically significant.

22 So far as can be judged from the average duration of symptoms, the respective numbers of patients symptom-free before and after treatment, and the incidence of congestive heart failure before and after treatment in the various treatment groups, the patients in the

various groups were approximately similar. That is, it does not appear that our reported deaths occurred only among patients desperately ill before treatment, and our reported success only among patients with less serious or less rapidly progressive lesions.

23 The occurrence of congestive heart failure before or after treatment is of serious prognostic import. In this connection, we present analyses of our material from several standpoints.

24 Twenty-one of the surviving 56 patients of this series are symptom-free and able to work, 26 have some persistent symptoms, but can carry on at light work, 9 are incapacitated. Twenty-eight of the 47 still able to work were well treated for syphilis.

25 Symptomatic relief in cardiovascular syphilis is frequently obtained, and its probability is in direct proportion to the amount of treatment given.

26 The occasional alteration of physical signs during or after treatment is discussed.

27 In an analysis from the standpoint of ability to work before and after treatment, well treated patients show up much more favorably than those untreated or badly treated.

28 Complete incapacity is much less frequent and of shorter duration in well treated than in poorly treated patients.

29 Fifty-seven of our 165 patients died of progressive cardiac failure, 28 (10 with aneurysm and 18 with aortic regurgitation) died suddenly, 11 are dead, but the cause of death is unknown, 13 died of some cause other than cardiovascular syphilis.

30 The arsenical drugs given to our patients are tabulated and the reactions to them analyzed. From these data we conclude that the arsenical drugs of choice are, in order, neoarsphenamine, bismarsen and silver arsphenamine. Old arsphenamine (606) should not be employed in patients with aneurysm or aortic regurgitation. The use of tryparsamide should be limited to patients with complicating neurosyphilis.

31 A fixed positive Wassermann reaction of the blood is the rule in cardiovascular syphilis, and the response of this reaction to treatment may be completely disregarded.

32 From the analysis of our material, we conclude that properly supervised antisyphilitic treatment, with adequate general medical care, given to patients with aneurysm or aortic regurgitation, prolongs life, alleviates symptoms, maintains the ability to pursue a gainful occupation and reduces the period of incapacity.

A POSSIBLE RELATIONSHIP OF PANCREATIC INSUFFICIENCY TO ADDISON-BIERMER (PERNICIOUS) ANEMIA

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AND
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As a result of the investigations of Whipple, Minot, Castle and others, the present conception of Addison-Biermer anemia is that it is a deficiency disease of a distinct type. An insufficient amount of some protein derivative is available for normal red blood corpuscle maturation, finally resulting in megaloblastic, macrocytic, hyperchromic anemia and hyperbilirubinemia. This lack of necessary protein derivative may be dependent in part on an inadequate intake of readily available protein, such as that contained in liver and stomach, and in part on inadequate digestion of less available protein-containing substances, such as beef. It has been contended by Castle and his co-workers¹ that the lack of normal protein digestion resulting in anemia is in some way due to the gastric achylia, although Castle has been unable to show what the necessarily missing factor is. He has shown by feeding experiments that it is not hydrochloric acid and not pepsin, that it is present in the gastric contents of patients without pernicious anemia, and that it has the properties of an enzyme. He has designated it as an unknown intrinsic factor. He felt that it was not contained in duodenal contents regurgitated into the stomach.

In 1929, Landau and Glass² reported a large series of miscellaneous cases in which they analyzed the fasting gastric contents and also the duodenal contents for pancreatic enzymes. Only nine of the whole series showed what the authors termed both gastric and pancreatic achylia. Eight of these were definite cases of Addison-Biermer anemia. Six of the eight had no trypsin at all, and the other two showed the extremely low amount of only 2 units. The ninth case was insufficiently studied to permit a diagnosis. More recently, Kunos and Gero³ have

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1 Castle, W B, Townsend, W C, and Heath, C W. *Am J M Sc* **180**: 305, 1930

2 Landau, A, and Glass, J. *Arch f Verdauungskr* **46** 192, 1929

3 Kunos, I, and Gero, S. *Gyógyászat* **70** 344, 1930

noted similar findings. As the fasting gastric content contains approximately the same concentration of pancreatic enzymes as the fasting duodenal content, except in hyperchlorhydria, we examined the fasting gastric contents of ten untreated patients with Addison-Biermer anemia for trypsin, and found it absent in nine. In the tenth case there was only 2.5 units. In sixty other cases, mostly with achlorhydria, trypsin was present in the contents of the fasting stomach in normal amounts. Although such a lack of trypsin secretion in cases of Addison-Biermer anemia is contrary to the findings in the two cases reported by McClure⁴ in 1922, it seems sufficiently striking to suggest a relationship to the inadequate protein digestion occurring in Addison-Biermer anemia.

Such a relationship is also suggested by the red blood macrocytosis occurring in diseases of the pancreas.⁵ The only conditions without marked anemia in which such a macrocytosis is found are the primary anemias, certain cases of jaundice and pancreatic disorders. In nine cases of cancer of the pancreas, all showed an erythrocyte macrocytosis ranging from 7.9 to 8.5 microns. In each of these cases our diagnosis was proved by operation or by autopsy. Landau and Glass² discussed cases both of definite pancreatic disease and of primary anemia.

If the secretion of trypsin is necessary for the normal digestion of proteins, and if its absence, which is rare, is associated with a primary type of anemia, it seems possible that its enzymic action is essential to the prevention of Addison-Biermer anemia. Trypsin might be the unknown intrinsic factor of Castle, not secreted by the stomach, but present owing to regurgitation from the duodenum. Normal human gastric juice, even though free from bile, contains trypsin, except when the stomach is emptying rapidly.⁶ In order to test such a hypothesis it was decided to duplicate Castle's feeding experiments with digested beef, but to use preparations of trypsin in solution to digest the meat instead of human gastric juice.

EXPERIMENTAL DATA

In each experiment we carried out, the trypsin-containing solution was made up to 300 cc. by the addition of distilled water, and incubated for two hours at 37 C. with 200 Gm. of fat-free beef ground up as hamburger steak. The resultant filtrate was passed through gauze and given the patient to drink, warm or cold. No difficulty was encountered in administering the digested beef solution to the patients, except in one case of an old woman. Feedings were carried out over periods varying from seven to twenty-three days. Each patient, with one exception

4 McClure, C. W., and Jones, C. M. *Boston M. & S. J.* **187**: 909, 1922.

5 von Boros, J. *Wien Arch. f. inn. Med.* **12**: 243, 1926.

6 Martin, Lay. *Biliary, Pancreatic and Duodenal Studies. Estimation of the Pancreatic Enzymes and Value of Such Determinations from a Clinical Standpoint*, *Arch. Int. Med.* **39**: 343 (March) 1927.

to be noted later, had a definite case of Addison-Biermer anemia, and responded in the usual way to adequate amounts of liver extract

Experiments in the Digestion of Beef by Solutions Containing Trypsin—As none of the experiments gave any positive results, they will be described only briefly. Pancreatin (Armour) was used as a beef digestant in three different cases without any effect on the red cell count, the hemoglobin determinations, the production of reticulocytes or the size of the cells as determined by the halometer.⁷ Each patient was fed for fourteen successive days. Bile with high trypsin content obtained from a human biliary fistula was used daily as a digestant for two weeks without effect, and pancreatic juice from the pancreatic fistula of a dog was equally ineffective over a seven day period. Dr. Nelson Howard performed the operation on the dog. A solution of powdered trypsin (Armour), with a strength of about 100 units (Gross) of enzyme activity, also failed to produce effective digestion of the beef.

These results demonstrated that a solution of trypsin alone was ineffective in the digestion of beef, so it was decided to try a solution more nearly simulating normal human gastric contents. As we wished to obtain protein digestion similar to that occurring physiologically, we employed both the proteolytic enzymes commonly found in the stomach contents.

Experiments in the Digestion of Beef by Solutions of Trypsin, Pepsin and Hydrochloric Acid—A solution of enzymes was made up which might be termed artificial gastric contents as far as protein digestion was involved. This consisted of 300 cc of distilled water to which approximately 1 Gm of powdered trypsin, 2 Gm of powdered pepsin (Armour) and from 2.5 to 3 cc of concentrated hydrochloric acid were added. This furnished a trypsin concentration of about 100 units, an adequate amount of pepsin in terms of Castle's similar work and a free acidity of from 90 to 100 degrees. The solution was thoroughly mixed by stirring, 200 Gm of ground beef was added, and incubation was carried out as in the previous experiments. The filtrate obtained was fed to two patients with Addison-Biermer anemia and to one patient with sprue with a blood picture of pernicious anemia. Four feeding experiments were carried out on the three patients, and a typical response to liver therapy was demonstrated in each during the stay in the hospital.

CASE 1—An old woman with arteriosclerosis, who was suffering from senile mental changes and diarrhea, had been failing clinically for one month before experiment 1 was started. She showed glossitis, hyperbilirubinemia with a negative direct van den Bergh reaction, absence of trypsin in the gastric contents during fasting and in the duodenal contents, and achlorhydria following the injection of histamine. The blood findings before, during and after treatment are shown in table 1. The first experiment consisted of eight consecutive feedings, and was then stopped so that the patient might be utilized for a second experiment. During the feedings she gained 9 per cent of hemoglobin and 590,000 red blood corpuscles in six days, the gain ceasing coincident with the cessation of therapy. The reticulocytes rose to 5 per cent on the seventh day, and the corresponding typical alteration in cell size⁸ developed its maximum on the seventh day. The blood count then

⁷ Cheney, G. California & West Med **34** 40, 1931

⁸ Fitzhugh, G., and Persons, E. L. J Clin Investigation **7** 631, 1927

remained practically stationary, the reticulocyte count returned to normal, and the average diameter of the erythrocytes returned to the original figure. After six days experiment 2 was started, and the patient was again fed, this time for a period of twenty-three days. During this experiment, the red cell and reticulocyte response were typical of that produced by the administration of slightly inadequate amounts of liver, as described by Minot and his co-workers,⁹ in that the erythrocyte count improved only a little, and there was a much prolonged but not intense response of the reticulated red cells. No improvement occurred after the cessation of therapy, and the reticulocyte count fell. The changes in red cell size were again comparable to those in the reticulocyte figures in this experiment.

TABLE 1—Results of Experiments 1 and 2 on the Blood Picture in a Case of Addison-Biermer Anemia and Pronounced Arteriosclerosis

	Red Blood Cells	Hemo- globin, per Cent	Reticu- loocytes, per Cent	Red Blood Cells, Diameter, Microns
Before 1st feeding				
27th day	2,100,000	40		8.0
9th day	1,520,000	36		8.0
3d day	1,230,000	34		8.0
During 1st feeding				
1st day	1,200,000	32	0.4	8.0
3d day	1,230,000	34		7.8
5th day	1,550,000	40	0.9	7.8
7th day	1,790,000	40	5.0	7.6
Before 2d feeding				
7th day	1,760,000	41	3.1	7.7
4th day	1,780,000	40	3.0	7.9
2d day	1,700,000	40	0.1	8.0
During 2d feeding				
1st day	1,760,000	40	0.1	8.0
4th day	1,700,000	40	1.6	7.8
6th day	1,700,000	40	4.0	7.6
8th day	1,600,000	40	3.6	7.7
9th day			3.7	7.7
11th day	1,500,000	40	4.0	7.6
12th day	1,500,000	40	5.0	7.7
13th day			5.1	7.8
14th day	1,570,000	40	5.8	7.8
18th day	2,170,000	45	5.0	7.9
20th day	2,090,000	45	5.0	8.0
23d day	1,860,000	43	4.0	8.0
After 2d feeding				
3d day	2,000,000	45	4.0	8.0
6th day	1,750,000	43	3.0	8.0

CASE 2—Experiment 3 was similarly carried out in a man 56 years old. The blood findings are shown in table 2. The icteric index was 14 units. The direct van den Bergh reaction was negative. The fasting gastric contents contained no trypsin. Gastric analysis after the injection of histamine failed to reveal any free acidity. A bone marrow puncture showed a typical picture of pernicious anemia. The Price-Jones curve was also typical. The blood count was stationary for nine days before the special therapy was instituted, which was continued for eleven days. There was a gain of approximately 1,000,000 red blood corpuscles and 20 per cent hemoglobin coincident with the special feedings. No reticulocyte response occurred, but the average diameter of the erythrocytes showed the characteristic changes, the smallest occurring on the eighth day.

⁹ Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A. *Am. J. M. Sc.* 175: 599, 1928. Minot, G. R., Murphy, W. P., and Stetson, R. P. *ibid.*, p. 581.

CASE 3—Experiment 4 was carried out on a German woman aged 60, who for three years, since living in Shanghai, had had recurrent attacks of glossitis, weakness with anemia and diarrhea with large, bulky stools. The blood showed macrocytic hyperchromic anemia with leukopenia identical with that found in Addison-Biermer anemia, and a bone marrow puncture showed an identical picture. There were 50 units of trypsin present in each of two samples of gastric contents obtained during fasting, and free acidity was found on three gastric analyses. The stools were characteristic of sprue. The blood findings before, during and after treat-

TABLE 2—Results of Experiment 3 on the Blood Picture in a Case of Addison-Biermer Anemia

	Red Blood Cells	Hemo- globin, per Cent	Reticu- loeytes, per Cent	Red Blood Cells, Diameter, Microns
Before feeding				
9th day	2,720,000	62	0.5	7.7
2d day	2,820,000	60	0.5	7.7
During feeding				
2d day	2,980,000	68	0.5	7.7
6th day	3,500,000	75	0.5	7.5
8th day	3,600,000	75	0.5	7.1
10th day	3,850,000	78	0.5	7.5
After feeding				
1st day	3,910,000	80		7.4
4th day	4,080,000	82		7.5

TABLE 3—Results of Experiment 4 on the Blood Picture in a Case of Sprue with a Typical Primary Type of Anemia

	Red Blood Cells	Hemo- globin, per Cent	Reticu- loeytes, per Cent	Red Blood Cells, Diameter, Microns
Before feeding				
22d day	1,500,000	47		
20th day	1,770,000	45		8.8
9th day	1,590,000	48		8.7
During feeding				
1st day	1,420,000	48	>0.5	8.6
5th day	1,400,000	50	4.0	8.6
8th day	1,380,000	50	3.0	8.3
12th day	1,800,000	52	1.0	8.4
15th day	2,032,000	57	0.5	8.5
After feeding				
2d day	2,238,000	58	>0.5	8.4
6th day	2,190,000	60	0.5	8.4
11th day	2,160,000	62	0.5	8.4
14th day	2,140,000	62	0.5	8.4

ment are recorded in table 3. It is noteworthy that the blood count was practically stationary for three weeks before the experiment was started.

As it has been shown that this type of sprue with anemia responds to treatment with liver extract in the same manner as does pernicious anemia,¹⁰ it was thought that if a sufficient amount of red blood corpuscle maturation factor could be produced by digesting beef, a similar response might be obtained. As both free hydrochloric acid and trypsin were present in this patient, the object was to introduce a larger amount of the necessary protein derivative than she could herself digest and absorb. She was fed for fifteen days in the same manner as the patients in cases 1 and 2. The hemoglobin rose 10 per cent, and the red blood count increased

10 West, Randolph. Porto Rico Rev. Pub. Health 3:4 219, 1927-1929.

800,000 cells by the second day after feeding was discontinued, and then remained approximately stationary for two weeks. The red blood count did not start to increase until after the ninth day of therapy, and gained on an average of 100,000 cells a day for eight consecutive days. The reticulocyte count rose to 4 per cent on the sixth day and gradually fell to less than 0.5 per cent on the fourteenth day. The average red cell diameter also diminished in the characteristic manner, reaching the lowest point on the ninth day.

Two further experiments were carried out in order to determine if only small amounts of trypsin would produce the same results as in the four preceding feeding tests. The solution was made up in the same way, containing the same amounts of water, pepsin and hydrochloric acid, but only enough trypsin was added to give a concentration of between 2.5 and 5 units. Such trypsin values are below the low limits of normal, and occur but rarely. This artificial gastric content, inadequate in trypsin, was used to digest the beef, and the resultant filtrate was fed to two patients with Addison-Biermer anemia. In the first case the feedings were continued for twelve consecutive days, and in the second case, for nine.

In the first of these two experiments the red blood cell count fell from 1,240,000 cells to 890,000 cells and the hemoglobin dropped from 35 to 32 per cent during the period of feeding. No reticulocyte response occurred. However, the diameter of the erythrocytes diminished from 8.1 to 7.8 microns on the eighth day, rising again to reach 8.2 microns on the twelfth day. In the second experiment the red blood cell count was practically stationary throughout the nine days. The initial figure was 1,560,000, and the figure on the ninth day was 1,380,000. The hemoglobin was 40 per cent throughout. No reticulocyte response occurred, however, the diameter of the erythrocytes diminished again, and subsequently increased, just as in patients fed with liver. Before the experiment the average diameter was 8.5 microns, falling by the seventh day to 7.6 microns, and subsequently rising to 8.4 microns.

COMMENT

It has been pointed out briefly that various solutions of trypsin alone were not effective in the digestion of beef. The product of digestion when fed to patients with Addison-Biermer anemia did not produce any changes in the blood picture. When a solution of pepsin, hydrochloric acid and trypsin comparable to that which might be obtained from a normal stomach was used as a digestant, something was produced from the beef, which when fed to the patient produced definite changes in the blood picture. As only human gastric contents have heretofore proved potent in such feeding experiments, the results obtained are worthy of careful analysis, even though the number of experiments is relatively small.

In each of the first four experiments with our artificial gastric contents, there was an improvement in the red blood cell count and hemoglobin during the feedings. The tables show that the counts were stationary before each experiment, and were again stationary subsequent to the experiment. During the first feeding in case 1, case 2 and case 3, the erythrocytes increased at a rate of about 100,000 a day during the period of improvement which is comparable to the rate of rise after liver therapy. In experiment 1 and in experiment 4 there

were reticulocyte rises of 5 and 4 per cent, respectively, and a change in red cell size, occurring at the same time during the feeding as that which occurs during successful liver therapy. In experiment 2 there was a prolonged reticulocyte response lasting about two weeks, and a rather delayed, but characteristic, alteration in erythrocyte diameters. In case 3, in which the initial red cell count was 2,820,000, no increase in reticulocytes occurred, but the changes in red cell size were pronounced. In the two cases in which very small amounts of trypsin were used, the blood was not improved, although changes occurred in the average diameter of the red corpuscles exactly like those in the other cases.

It is noteworthy that in each of four experiments in cases of hyperchromic macrocytic anemia of the so-called primary type, feedings of beef digested with artificial gastric contents, containing pepsin, hydrochloric acid and trypsin, produced changes in the blood comparable to those obtained by Castle when using human gastric contents to digest beef, except that there was a less pronounced reticulocyte response. It is of real significance that in each instance improvement in the red cell count and hemoglobin percentage, reticulocytosis and changes in the diameters of the red cells appeared coincident with the feedings, and ceased after the feedings were discontinued. Under such circumstances there can be little doubt that something was produced from the beef during the process of digestion that acted in the same way as the erythrocyte maturation factor contained in liver. As all the same changes in the red cell counts, the hemoglobin percentage, the reticulocyte percentage and the cell size occurred just as they take place during liver therapy, the same maturation factor must have been elaborated by digestion of the beef. The difference is that the changes are not all of the same magnitude as in adequate liver therapy, but duplicate the changes found when barely enough or not quite enough liver is fed. In other words, the maturation factor was produced, but not in sufficient quantity when compared to the successful administration of liver. Assuming that digested beef can yield as much maturation factor as is contained in a like amount of liver, and certain of Castle's most successful experiments show that this is possible, many reasons may be advanced why our results are not as good as Castle's best or as good as those obtained with adequate liver treatment. Briefly, the following points are worthy of mention. Only 200 Gm of beef were used, whereas at least 300 Gm of liver are usually necessary. No special measures were taken to divide the beef muscle finely, as in Castle's experiments. No attempt was made during incubation to assure either optimum peptic or tryptic activity. A powdered preparation of trypsin was used which may have been inadequate in amount to complete diges-

tion, and which may not have been exactly comparable to the freshly activated enzyme in normal duodenal contents. Also, the patient in case 1 showed marked arteriosclerosis, which seems to be a barrier to the usually effective method of treatment, in that a larger dosage is required.¹¹ These points do not bear discussion at present and can be settled only by the results of further experiments. The important point to be made now is that *some maturation factor was produced*.

Returning to the original hypothesis that pancreatic insufficiency, notably a lack of trypsin production, is possibly related to the cause of Addison-Biermer anemia, just what do the results of our feeding experiments demonstrate? They show that tryptic digestion alone is no more effective than pepsin and hydrochloric acid alone, which was shown by Castle.¹ However, both these proteolytic enzymes together in solution are capable of producing from beef the substance necessary to bring about a remission in a case of macrocytic hyperchromic anemia. Furthermore, if very small amounts of trypsin are used with the activated pepsin, no remission occurs. If there is, then, an inadequate production of trypsin in a case of Addison-Biermer anemia during the stage of exacerbation, as well as a gastric achylia, and if beef digested by active pepsin and trypsin is capable of producing a remission in such a case, it seems probable that the fundamental disorder in Addison-Biermer anemia is a pancreatic insufficiency superimposed on gastric achylia, resulting in deficient protein digestion which is responsible for the anemia. Trypsin would then represent the unknown intrinsic factor of Castle, or, to be more accurate, the unknown extragastric factor of Morawitz.¹²

We have not proved such a hypothesis, but have made this preliminary report on the results of a few experiments in order that it may be more rapidly proved or disproved by the work of others, particularly as cases of untreated pernicious anemia suitable for necessary experimentation are now so rarely encountered. A great many questions will be raised about such a conception of the cause of Addison-Biermer anemia, which cannot be dealt with at present, but will be considered in a subsequent report.

SUMMARY

1 The present conception of Addison-Biermer anemia is that it is a deficiency disease due to an inadequate supply of a protein derivative necessary to normal maturation of red blood cells.

2 As a result of successful experiments in feeding beef digested with normal human gastric contents to patients with Addison-Biermer

11 Beebe, R. T., and Lewis, G. E. *Am J M Sc* **181** 796, 1931

12 Morawitz, P. *Arch f Verdauungskr* **47** 305, 1930

anemia, Castle has concluded that the cause of the disorder is dependent on the gastric achylia. The nature of this supposed gastric defect has remained unproved, and he has termed it the unknown intrinsic factor.

3 Recent studies of the gastric contents during fasting and duodenal contents strongly suggest that in cases of Addison-Biermer anemia there is a marked insufficiency of the pancreatic enzymes, notably trypsin, in addition to the gastric achylia. The macrocytosis characteristic of this anemia has also been frequently observed in pancreatic disorders.

4 Feeding experiments in which solutions of trypsin were used to digest beef have failed to produce any effect on the blood findings in cases of Addison-Biermer anemia.

5 Feeding experiments in which an artificial gastric content containing hydrochloric acid, pepsin and trypsin was used to digest beef have in three instances in two cases of Addison-Biermer anemia and in one instance in a case of sprue with a similar blood picture produced changes in the red blood cell count, hemoglobin determinations and reticulocyte response similar to those obtained by Castle.

6 Changes in the average diameter of the red cells characteristic of a beginning remission after liver therapy occurred in these four instances and also in two others when very small amounts of trypsin were used. No other evidence of improvement in the blood findings was detected in the last two cases.

7 Our feeding experiments show that beef digested by hydrochloric acid, pepsin and trypsin yields the erythrocytic maturation factor necessary to produce all the blood changes characteristic of a remission in pernicious anemia. The changes demonstrated are not as pronounced as those in adequate liver therapy, but are on the whole more like those in inadequate treatment with liver.

8 It seems probable that the protein derivative deficiency in Addison-Biermer anemia is due to a lack of both peptic and tryptic digestion. Trypsin would then represent the unknown intrinsic factor of Castle.

THIOCYANATE THERAPY IN HYPERTENSION

II ITS EFFECT ON BLOOD PRESSURE

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The reintroduction of thiocyanate in the treatment for arterial hypertension has, in recent years, attracted wide attention. A number of investigators have attested to its effectiveness in lowering both normal and abnormally elevated blood pressures¹. On the other hand, it has been stated that in a large group, thiocyanate appears to exert no more beneficial effect on hypertension than do certain so-called nonspecific measures of therapy, classed under the general heading of "psychic and sedative treatment"². We have shown in a previous study³ that thiocyanate administered in the dosage frequently recommended may be accompanied by serious toxic manifestations and even death. Furthermore, the great tendency toward variability of raised blood pressures⁴ and the not infrequent spontaneous remissions observed in the course of essential hypertension⁵ often render the true interpretation of any so-called therapeutic endeavor particularly hazardous. It therefore

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1 Gager, L. T. The Incidence and Management of Hypertension, with a Note on Sulphocyanate Therapy, *J. A. M. A.* **90** 82 (Jan 14) 1928. Westphal, K., and Blum, R. Rhodan Treatment of Genuine High Arterial Pressure and the Theoretical Foundation for It, *Deutsches Arch. f. klin. Med.* **152** 331, 1926. Nichols, J. B. Pharmacologic and Therapeutic Properties of the Sulphocyanates, *Am. J. M. Sc.* **170** 735 (Nov) 1925.

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3 Goldring, W., and Chasis, H. Thiocyanate Therapy in Hypertension. I. Observations on Its Toxic Effects, *Arch. Int. Med.* **49** 321 (Feb) 1932.

4 Mosenthal, H. O., and Short, J. J. The Spontaneous Variability of Blood Pressure and the Effects of Diet upon High Blood Pressure with Special Reference to Sodium Chloride, *Am. J. M. Sc.* **165** 53, 1923. Diehl, H. S. The Variability of Blood Pressure. Morning and Evening Studies, *Arch. Int. Med.* **43** 835 (June) 1929.

5 Ayman, D. Normal Blood Pressure in Essential Hypertension, *J. A. M. A.* **94** 1214 (April 19) 1930.

seemed advisable to us that another series of observations be added to those reported by other investigators, in order to add to the sum total of such observations and to determine, if possible, the range of effective dosage by interpreting as effective only distinctly unequivocal instances of lowering of blood pressure, finally, to make such observations on the excretion of thiocyanate in individual patients as were deemed necessary in order to arrive at a quantitative estimate of the amount of residual drug in the body at the time of its first observed effect on the blood pressure

PLAN OF STUDY AND METHOD

Fifty patients with hypertension were selected and subjected to seventy-four different trials with thiocyanate therapy. Of these trials, sixty-nine were with patients who had hypertension of the essential type and five were with patients whose hypertension was associated with chronic diffuse glomerulonephritis. Forty-four trials were made in the outpatient clinic and thirty were made during a stay in the hospital wards. All blood pressure readings were made by the same group of observers. Readings were consistently taken on the right arm only, and a standard mercury manometer was used exclusively. The auscultatory method was invariably employed. A sufficient period of mental and physical rest was uniformly insisted on before blood pressure readings were made. With the arm cuff in position, five and often more readings were made before the blood pressure level was decided on. When for any reason doubt existed or when a decided change from the previous reading was noted, two and usually three observers made independent readings before a final estimate of the blood pressure level was accepted. While on thiocyanate therapy, outpatients were seen weekly and ward patients at least once daily.

Being aware of the great tendency toward spontaneous variability of blood pressure levels, control periods were extended as long as feasible, and as many blood pressure readings were made as we believed were necessary on each patient. The length of the control period was principally determined by the history of known duration of the hypertension and the degree of variability of the blood pressure noted under our own observation. That is, the longer the history of hypertension as obtained from the patient and the less the variability of the blood pressure under our observation, the relatively shorter control period seemed necessary.

Both the sodium and potassium salts were used indiscriminately in our series, and no record was kept of the particular salt administered to each patient. Such a record did not seem necessary in view of the evidence that the effective radical is the thiocyanate⁶

⁶ Nichols (footnote 1, third reference)

The principal purpose of this study was to investigate the depressor effect of thiocyanate on the blood pressure in persons with hypertension. It was necessary then to decide on some criterion by which this effect could be measured. Two alternatives presented themselves. The first criterion that suggested itself was a predetermined fall, in millimeters of mercury, in both systolic and diastolic pressures. It was obvious early in our study that this criterion of effect would not be wholly adequate, because even appreciable falls in blood pressure from a very high pretreatment level might not constitute a satisfactory clinical reduction, as, for example, a fall in systolic pressure from 260 to 210 mm of mercury or a fall in diastolic pressure from 140 to 115 mm. Moreover, there are instances in which a considerable and persistent fall from the control level occurs in the systolic pressure, whereas the fall in the diastolic pressure is insignificant. This occurrence is not infrequent when the pretreatment level of the systolic pressure is considerably elevated above normal and the diastolic only slightly. Such a response, we believe, must obviously be accredited to the therapy employed, but if the aforementioned criterion were used, it would have to be regarded as an unsuccessful trial. The second alternative was to use as a criterion a definite level of systolic and diastolic blood pressures, a fall to or below which, after treatment, would be termed a successful depressor effect. We decided to use this criterion and selected arbitrarily the level of 165 systolic and 100 diastolic. On the face of it, it may appear that in some instances the therapy was considered as effective even though only slight falls occurred from the control level of pressure to the "criterion" level. Actually, as the tables show, this was not the case. The average of all "successful" falls in systolic pressure amounted to 45 mm of mercury and in the diastolic pressure it amounted to 31 mm.

The method employed in estimating the quantitative excretion of thiocyanate in the urine and its accuracy as compared with the method described by Schreiber⁷ were noted in a previous paper by us.³

In order to evaluate further the effectiveness of thiocyanate as a depressor drug, strict interpretation was applied to the meaning of the term "trial." In the early part of the study a "trial" was considered complete only when the drug had lowered blood pressure, in accordance with our stated criteria, or when toxic symptoms occurred. The relatively frequent occurrence of toxic manifestations in our early cases suggested the necessity for modifying our stand in the interests of safety to the patient. Accordingly in the patients studied in the latter part of this series a "trial" was considered complete if neither thera-

⁷ Schreiber, H. Thiocyanate Content of Human Blood Serum, *Biochem Ztschr* **163** 241, 1925

peutic nor toxic effect occurred when 0.163 Gm ($2\frac{1}{2}$ grains) had been given for seventy-seven consecutive days or more, if 0.326 Gm (5 grains) had been given for eighteen consecutive days or more or if 0.652 Gm (10 grains) had been given for twelve consecutive days or more. In the three instances in which 1 Gm or more was given daily,

TABLE 1—*Results of Treatment with Thiocyanate in Essential Hypertension Ambulatory Group*

No	Age	Blood Pressure Control		Control Period, Days	Lowest Blood Pressure after Treatment	Thiocyanate Intoxication	Effective in Lowering Blood Pressure
		Range, Mm Hg	Average, Mm Hg				
1	54	220/110 to 198/104	213/107	126	150/ 85	No	Yes
2	54	220/110 to 190/104	190/104	161	165/ 90	No	Yes
3	64	220/120 to 185/100	205/109	35	140/ 70	No	Yes
4	65	230/138 to 175/104	203/116	294	190/ 92	Yes	No
5	46	260/130 to 210/110	232/120	378	185/ 95	No	No
6	56	205/120 to 170/ 98	180/105	231	135/ 70	Yes	Yes
7	37	240/140 to 188/106	203/122	273	158/ 95	No	Yes
8	53	236/156 to 193/120	220/136	182	157/ 90	No	Yes
9	53	215/125 to 175/115	196/117	35	150/ 75	No	Yes
10	53	205/120 to 174/105	190/113	14	145/ 90	No	Yes
11	29	268/132 to 180/132	206/132	133	180/125	No	No
12	29	268/132 to 180/132	198/132	163	185/125	Yes	No
13	29	268/132 to 180/132	190/130	203	150/110	No	No
14	50	210/120 to 160/108	174/112	33	155/ 95	No	No
15	42	250/160 to 132/ 80	187/122	53	207/127	No	No
16	38	182/145 to 168/135	177/140	14	180/125	No	No
17	58	212/122 to 196/109	203/116	84	165/105	No	No
18	61	224/130 to 198/110	210/119	35	192/105	No	No
19	62	240/125 to 200/ 96	217/109	91	158/ 90	No	Yes
20	51	222/142 to 216/140	218/141	28	184/112	No	No
21	46	250/118 to 195/100	222/109	62	184/ 90	No	No
22	64	210/ 88 to 190/ 88	198/ 88	32	150/ 75	No	Yes
23	53	230/125 to 170/110	206/121	48	170/ 98	No	No
24	40	250/130 to 232/120	239/123	42	186/106	No	No
25	46	225/110 to 184/ 96	209/103	84	190/100	No	No
26	62	206/100 to 188/ 92	200/ 96	28	164/ 82	No	No
27	65	212/110 to 160/ 90	186/101	111	178/ 94	No	No
28	54	212/104 to 198/ 94	206/ 97	42	170/ 90	No	No
29	45	200/128 to 185/102	192/115	56	174/ 96	No	No
30	54	210/118 to 165/100	182/100	133	183/108	No	No
31	42	199/125 to 190/108	196/116	21	178/110	No	No
32	51	250/158 to 184/110	243/129	203	164/120	No	No
33	65	250/140 to 180/ 98	200/110	67	156/ 96	No	No
34	62	235/130 to 180/115	208/123	28	215/110	No	No
35	46	260/130 to 185/ 92	215/110	469	166/ 90	No	No
36	64	215/120 to 160/180	200/105	28	150/ 72	No	No
37	63	230/138 to 175/ 95	205/110	220	190/ 90	No	No
38	54	220/120 to 165/100	195/105	168	175/108	No	No
39	46	250/118 to 170/ 94	185/102	54	176/110	No	No
40	64	216/ 96 to 184/ 78	199/ 88	91	142/ 70	No	Yes
41	50	218/126 to 212/122	215/124	7	182/100	No	No
42	53	220/120 to 170/ 98	180/110	90	200/112	No	No
43	40	234/128 to 186/106	205/105	180	186/104	No	No
44	56	230/125 to 180/100	209/119	360	190/ 90	Yes	No

the drug was discontinued because of toxic symptoms in two and a fall in blood pressure in one. In every instance in which we discontinued thiocyanate before either a therapeutic or a toxic effect occurred, the total amount that had been administered was with few exceptions, greater than the amount frequently reported by others as an effective dosage.

RESULTS

Tables 1 and 2 give a summary of the results of treatment with thiocyanate in an ambulatory and a hospitalized group of patients with

essential hypertension There were forty-four trials in the ambulatory group and twenty-five trials in the hospital group The ages ranged from 29 to 65 years The period of control in the ambulatory group ranged from seven to three hundred and seventy-eight days and in the hospital group from five to one hundred and five days It will be noted

TABLE 2—Results of Treatment with Thiocyanate in Essential Hypertension Hospitalized Group

No	Age	Blood Pressure Control		Control Period, Days	Lowest Blood Pressure after Treatment	Thiocyanate Intoxication	Effective in Lowering Blood Pressure
		Range, Mm Hg	Average, Mm Hg				
1	50	210/120 to 160/105	174/112	15	160/100	No	No
2	53	232/134 to 198/125	209/129	8	120/ 70	No	Yes
3	46	208/120 to 190/105	194/114	35	170/110	No	No
4	57	230/130 to 186/ 92	202/113	11	118/ 90	Yes	Yes
5	53	236/134 to 196/120	220/113	16	146/ 74	No	Yes
6	53	230/130 to 220/106	224/113	7	210/120	Yes	No
7	55	180/105 to 158/ 95	174/102	12	115/ 80	No	Yes
8	56	220/130 to 190/100	207/110	8	155/ 90	Yes	Died*
9	40	225/130 to 204/100	237/112	13	204/ 88	Yes	Died*
10	63	210/146 to 190/128	202/133	5	140/ 80	Yes	Yes
11	50	250/155 to 216/120	230/130	18	180/100	No	No
12	50	230/130 to 186/100	205/110	47	190/120	Yes	No
13	63	240/168 to 190/128	215/145	31	138/ 70	No	Yes
14	52	228/138 to 208/104	221/122	8	182/ 90	No	No
15	55	250/140 to 198/120	227/137	12	180/100	No	No
16	55	250/140 to 180/ 98	200/110	105	210/114	Yes	No
17	49	260/140 to 190/ 96	204/114	25	180/ 98	No	No
18	43	198/132 to 170/112	181/126	14	148/ 86	No	Yes
19	46	200/100 to 185/ 95	187/109	36	162/ 92	No	No
20	48	208/118 to 178/108	195/115	13	186/ 98	No	No
21	44	168/114 to 154/ 92	159/103	0	162/ 90	Yes	No
22	54	264/132 to 240/120	253/128	9	164/ 84	Yes	Yes
23	51	182/120 to 162/ 98	173/ 98	19	140/ 88	No	No
24	48	198/160 to 184/ 98	200/119	17	184/ 96	No	No
25	51	250/138 to 192/118	221/124	11	196/110	No	No

* Death was due to thiocyanate poisoning *

TABLE 3—Results of Treatment with Thiocyanate in Nephritic (Chronic Diffuse Glomerulonephritis) Hypertension

No	Age	Blood Pressure Control		Control Period, Days	Lowest Blood Pressure after Treatment	Thiocyanate Intoxication	Effective in Lowering Blood Pressure
		Range, Mm Hg	Average, Mm Hg				
1	21	220/140 to 180/120	196/130	7	114/ 64	No	Yes
2	44	290/180 to 234/156	290/165	9	138/ 95	No	Yes
3	47	248/160 to 202/125	229/141	8	160/100	No	Yes
4	60	210/110 to 176/ 90	195/ 98	150	194/ 86	No	No
5	60	210/110 to 176/ 90	195/ 95	143	170/ 86	No	No

that a "trial" was considered effective when the blood pressure fell to or below 165 systolic and 100 diastolic, that is, the arbitrarily chosen criterion There are instances (see cases 20, 24 and 41, table 1, and cases 11, 14 and 15, table 2) in which marked falls in both systolic and diastolic pressures occurred, but the blood pressure remained distinctly above 165 systolic and 100 diastolic, and no improvement occurred in the subjective symptoms In order to adhere to our strict standard of criteria for effect all these instances, because of the difficulty of their

interpretation, were considered ineffective. Table 3 shows the effect of thiocyanate on the hypertension of chronic diffuse glomerulonephritis. It represents five trials on four patients. It is interesting, even in the small number, that notwithstanding reports to the contrary, thiocyanate carefully administered appears just as likely to be effective and no more likely to produce toxicity in patients with glomerulonephritis than in patients with essential hypertension. In this group, care was taken not to include patients during an acute exacerbation because of the possibility of an accompanying spontaneous fall of blood pressure as the acute condition subsides. It may seem that the control period of from seven to nine days in the so-called "effective" cases was too short to be conclusive. But that thiocyanate did actually lower the blood

TABLE 4—*Persistence of Hypotensive Effect of Thiocyanate*

No	Type of Hypertension	Average Daily Dose, Gm	Total Dose, Gm	Persistence, Days
Ambulatory group				
1	Essential	0.326	8.48	28
2	Essential	0.326	10.76	26
3	Essential	0.652	13.69	49
4	Essential	0.326	15.98	34
5	Essential	0.326	29.35	110
6	Essential	0.489	31.96	55
7	Essential	0.326	33.66	48+
8	Essential	0.489	75.50	41
Hospitalized group				
9	Essential	0.326	4.56	28+
10	Essential	0.652	8.48	15+
11	Nephritic	0.652	9.29	14
12	Nephritic	0.978	10.43	73+
13	Essential	1.192	26.35	7
14	Essential	0.613	31.14	32

pressure in at least one patient was obvious from the fact that the blood pressure returned to its original level fourteen days after the drug was discontinued. In the two other patients the blood pressure remained low up to the time the patients left the hospital at their own request.

Table 4 represents follow-up observations on fourteen patients in whom the blood pressure was effectively lowered by thiocyanate and the duration of the hypotensive effect after discontinuance of the drug. The hypotensive effect in this group of patients persisted for from seven to one hundred and ten days, at which time the blood pressure had returned to or nearly to its control level. There seemed to be no constant relationship between the persistence of the artificially lowered blood pressure and the amount of thiocyanate required to produce the lowering.

Table 5 serves to indicate that the effect of thiocyanate cannot be logically anticipated from the average daily dose or the duration of medication. It will be seen that a "trial" was considered completed when

TABLE 5—*Relation of the Dosage of Thiocyanate to the Effect on Blood Pressure and the Occurrence of Toxic Manifestations*

No	Type of Hypertension	Blood Pressure Lowered to or Below 165/100, Mm Hg	Average Daily Dose, Gm	Duration of Medication, Days	Total Dose, Gm	Toxic Effect
1	Essential	Yes	0.326	14	4.56	No
2	Essential	Yes	0.652	7	4.56	No
3	Essential	Yes	0.326	14	4.56	No
4	Essential	No	0.326	18	5.87	No
5	Essential	No	0.652	9	5.87	Psychosis
6	Essential	No	0.978	7	6.85	No
7	Essential	No	0.326	25	8.15	No
8	Essential	No	0.815	10	8.15	Nausea, vomiting
9	Essential	Yes	0.326	27	8.80	No
10	Essential	No	0.326	28	9.13	No
11	Essential	No	0.652	14	9.13	No
12	Essential	Yes	0.326	28	9.13	Psychosis
13	Essential	Yes	0.978	10	9.78	No
14	Essential	No	0.652	15	9.78	Death*
15	Essential	No	0.326	33	10.76	No
16	Essential	No	0.405	28	11.34	Fatigue
17	Essential	No	1.620	7	11.34	Psychosis
18	Essential	Yes	0.326	35	11.41	No
19	Essential	No	0.326	35	11.41	No
20	Essential	No	0.326	35	11.41	No
21	Essential	No	0.170	69	11.73	Dermatitis
22	Essential	No	0.978	12	11.74	No
23	Essential	No	0.978	12	11.74	No
24	Essential	No	0.163	77	12.55	No
25	Essential	No	0.978	13	12.71	Psychosis
26	Essential	No	0.326	40	13.04	No
27	Essential	No	0.652	20	13.04	No
28	Essential	No	0.326	40	13.04	No
29	Essential	Yes	0.691	19	13.13	No
30	Essential	No	0.326	42	13.69	No
31	Essential	Yes	0.652	21	13.69	No
32	Essential	No	0.326	42	13.69	No
33	Essential	No	0.326	42	13.69	No
34	Essential	Yes	0.326	43	14.01	Fatigue, nausea
35	Essential	Yes	0.805	18	14.49	Death*
36	Essential	No	0.326	49	15.97	No
37	Essential	Yes	0.326	49	15.97	No
38	Essential	No	0.489	35	17.11	Fatigue, nausea
39	Essential	No	0.326	55	17.93	No
40	Essential	No	0.652	28	18.26	No
41	Essential	No	0.652	28	18.26	No
42	Essential	No	0.163	121	19.72	No
43	Essential	No	0.326	63	20.54	No
44	Essential	Yes	0.326	66	21.51	No
45	Essential	Yes	0.326	69	22.49	No
46	Essential	Yes	0.326	70	22.82	No
47	Essential	No	0.326	71	23.15	No
48	Essential	No	0.163	148	24.12	No
49	Essential	No	0.326	75	24.45	No
50	Essential	No	0.326	77	25.10	No
51	Essential	No	0.326	77	25.10	No
52	Essential	Yes	0.326	78	25.42	No
53	Essential	No	0.489	52	25.43	No
54	Essential	No	0.648	41	26.57	No
55	Essential	Yes	1.210	22	26.62	Psychosis
56	Essential	No	0.652	41	26.73	No
57	Essential	No	0.652	42	27.38	No
58	Essential	No	0.326	84	27.38	No
59	Essential	No	0.652	42	27.38	No
60	Essential	No	0.652	49	31.95	No
61	Essential	Yes	0.638	51	32.54	Psychosis
62	Essential	No	0.652	50	32.60	No
63	Essential	Yes	0.978	35	34.27	No
64	Essential	Yes	0.652	55	35.86	No
65	Essential	No	0.652	55	35.86	No
66	Essential	No	0.578	78	45.08	No
67	Essential	No	0.652	74	48.25	No
68	Essential	No	0.652	100	65.20	No
69	Essential	No	0.326	203	66.18	No
70	Glomerulonephritis	Yes	0.326	19	6.19	No
71	Glomerulonephritis	Yes	0.978	10	9.78	No
72	Glomerulonephritis	Yes	1.080	10	10.80	No
73	Glomerulonephritis	No	0.326	64	20.86	No
74	Glomerulonephritis	No	0.652	76	49.55	No
1	Normal blood pressure	Yes†	0.652	5	3.26	No
2	Normal blood pressure	Yes†	0.326	14	4.56	No
3	Normal blood pressure	Yes†	0.978	5	4.89	No
4	Normal blood pressure	Yes†	0.326	36	11.74	No

* Death due to thiocyanate poisoning

† The fall after treatment with thiocyanate was unequivocal and persistent for from two to ten days

the blood pressure fell in accordance with our stated criterion, when toxic symptoms occurred or when the total amount of thiocyanate administered was in most instances distinctly greater than the amount usually recommended by others as therapeutically effective⁸ The latter course, namely, discontinuance of the thiocyanate before either therapeutic or toxic manifestations occurred after a relatively large dose had been administered, seemed imperative to us because of our previous experience with the toxicity of thiocyanate³ The toxic manifestations noted in this table are fully described in the study referred to This table further indicates the frequency with which thiocyanate may lower normal blood pressure

In table 6, the data of the preceding table are condensed and summarized They represent an evaluation of the clinical usefulness of various dosages of thiocyanate The absence of therapeutic effect with

TABLE 6—*Effectiveness of Thiocyanate with Various Daily Dosages*

Daily Dose, Gm	Number of Trials	Blood Pressure Lowered to or Below 165/100, Mm Hg	Effectiveness, per Cent	Number of Toxic Cases	Thiocyanate Intoxication, per Cent	Number of Fatal Cases Due to Thiocyanate Poisoning
0.163 (2½ grains)	4	0	0	1*	25	0
0.326 (5 grains)	34	12	35.2	3	8.8	0
0.489-0.815 (7½-12½ grains)	26	6	23	6	23	2
0.978-1.63 (15-25 grains)	10	5	50	3	33.3	0

* Maculopapular dermatitis

0.163 Gm (2½ grains) daily administered from seventy-seven to one hundred and forty-eight days in four patients seemed sufficient reason for considering it an ineffective dosage The great frequency of toxic manifestations with from 0.978 to 1.62 Gm (from 15 to 25 grains) given daily in ten trials was sufficient evidence for considering this dosage harmful The dosage of from 0.489 to 0.815 Gm daily (from 7½ to 12½ grains) was accompanied by toxic manifestations in the same percentage as it produced satisfactory lowering of the blood pressure Moreover, two fatalities occurred in this group as a result of thiocyanate poisoning The highest percentage of effectiveness with the lowest incidence of toxicity was observed in those patients who received 0.326 Gm (5 grains) daily

The data in table 7 indicate the relative excretion rate of thiocyanate in patients with essential hypertension and in patients with the hyper-

⁸ Gager (footnote 1, first reference) Palmer, R. S., Silver, L. S., and White, P. D. The Clinical Use of Potassium Sulphocyanate in Hypertension, *New England J. Med.* **201**:709 (Oct. 10) 1929 Borg, J. F. Use of Sulphocyanates in Treatment of Hypertension, *Minnesota Med.* **13**:281 (May) 1930

tension of chronic diffuse glomerulonephritis Furthermore, when the same amount of thiocyanate was administered in a single dose to a "normal" person and one with chronic diffuse glomerulonephritis, the "normal" person excreted an average daily amount twice as great as did the patient with nephritis It would seem from these observations that the ease with which thiocyanate is excreted bears a direct relation-

TABLE 7—*A Comparison of the Excretion Rate of Thiocyanate in Essential Hypertension and Nephritic Hypertension**

No	Type of Hypertension	Average Daily Dose, Gm	Average Thiocyanate Excretion, Gm per 24 Hr
1	Nephritic	0.978	0.097
2	Nephritic	1.004	0.277
3	Nephritic	0.652	0.250
4	Essential	0.978	0.540
5	Essential	0.915	0.557
1	Normal	1.143 (single dose)	0.088
2	Nephritic	1.143 (single dose)	0.043

* Chronic diffuse glomerulonephritis

TABLE 8—*Excretion Time of Thiocyanate (Single Dose)*

Diagnosis	One Dose, Gm	Days Necessary for Complete Excretion
Normal*	0.163	5
Normal	0.163	4
Normal	0.163	4
Normal	0.163	4
Normal	0.326	9
Normal	0.652	11
Normal	1.143	14
Nephritic†	1.143	22

* No evidence of organic disease

† Chronic diffuse glomerulonephritis

TABLE 9—*Summary of Results of Treatment with Thiocyanate*

	Number of Trials	Blood Pressure Lowered to or Below 165/100, Mm. Hg	Effectiveness in Lowering Blood Pressure, per Cent	Toxic	Deaths Due to Thiocyanate Poisoning ³
"Normal"*	4	4	100	0	0
Essential hypertension	69	20	28.9	13	2
Nephritic hypertension	5	3	60	0	0
Hypertension, total	74	23	31	13	2

* In this group of persons with "normal" blood pressure the fall after treatment with thiocyanate was unequivocal and persistent for from two to ten days

ship to the functional integrity of the kidney Likewise, there appears to be a distinct lack of relationship between the average amount excreted per day and the average amount administered per day The slow excretion rate of thiocyanate in the presence of glomerulonephritis is reflected in the prolongation of its time for complete excretion as

compared with a "normal" person. This is shown in table 8. The remaining data in this same table clearly indicate that the days necessary for complete excretion of the drug are roughly proportional to the total amount administered. The observation that at least four days are necessary for the complete excretion of a single dose as small as 0.163 Gm ($2\frac{1}{2}$ grains), in persons with normal renal function, is striking evidence of the great ease with which thiocyanate accumulates in the body on continuous administration over a period of time.

Table 9 is a summary of the results of thiocyanate administration in the entire group studied. The blood pressure was definitely and effectively lowered in 31 per cent of all hypertensive cases observed. The fall in blood pressure was almost invariably associated with improvement in subjective symptoms. The higher percentage of effectiveness in the group with glomerulonephritis has little significance in view of the small number observed. The toxic and fatal cases noted in this table were fully discussed in a previous paper.⁹

COMMENT

In recent years a number of substances have been advocated as useful in artificially lowering the blood pressure in hypertension.⁹ Their effectiveness in this regard has not been generally confirmed. Thiocyanate, on the other hand, has met with approval among a large number of independent investigators. One fact seems true from our data: thiocyanate will effectually lower blood pressure in one of about every three persons with hypertension. Our percentage of effectiveness is lower than that observed by many other investigators. Almost invariably, a fall in blood pressure was accompanied by subjective improvement. However, subjective improvement occurred in many patients on thiocyanate therapy in whom no lowering of blood pressure occurred. This led us to believe that such improvement was largely psychic. Still, exclusive of toxic effects from the drug itself, no obvious harmful effects were noted from persistent lowering of a previously high blood pressure. Whether or not harmful effects occurred that were not immediately obvious, we cannot say from the data available.

When it is thought that thiocyanate may be useful in a given patient, the dose should not exceed 0.362 Gm (5 grains) daily. However, the uncertainty of its effect is evidenced by the fact that such daily dosage

⁹ Macdonald, W. J. Extractives of Liver Possessing Blood Pressure Lowering Properties, *Canad. M. A. J.* **15**:697, 1925. Barksdale, I. S. Studies on the Blood Pressure Lowering Principle in the Seed of the Watermelon (*Cucurbita Citrullus*), *Am. J. M. Sc.* **171**:111, 1926. Stieglitz, E. J. Bismuth Subnitrate in the Treatment of Arterial Hypertension, *J. A. M. A.* **95**:842 (Nov. 12) 1930.

may be effective in lowering blood pressure in as short a period as fourteen days or it may be necessary to continue it as long as seventy-eight days. At the first indication of toxic effect (fatigue, nausea or vomiting) or the first distinct fall in blood pressure, the drug should be discontinued. When the blood pressure, having responded by a satisfactory fall, returns to its original high level, thiocyanate may be safely readministered only when ferric chloride added to the acidified urine indicates that the drug has been entirely excreted. If the blood pressure does not show a satisfactory fall after 26.16 Gm (5 grains daily for eighty days) has been taken, our data indicate that with few exceptions it is useless to continue the treatment.

The foregoing scheme of dosage is purely arbitrary and based on a consideration of our entire series as a group. However, in considering individual patients, it must be concluded that there is no constant dosage at which either a toxic or a therapeutic effect may be anticipated. Some of the inconstancies observed are illustrated by the following observations. One patient who responded, by a fall in blood pressure, to 0.326 Gm (5 grains) daily on three successive occasions failed subsequently to respond to a repetition of treatment with the same dosage over a similar period of time. Another patient who responded, by a satisfactory fall in blood pressure, to 0.326 Gm (5 grains) given daily on two different occasions failed subsequently to respond to 0.652 Gm (10 grains) daily given over a comparable period of time. A third patient who responded satisfactorily after a total dose of 13.2 Gm (202 grains) subsequently became severely toxic (hallucinations of sight and hearing, disorientation, etc.) on a total dose of 12.74 Gm (195 grains).

It is this uncertainty regarding proper dosage, coupled with the fact that frequently there is slight if any difference between the amounts that produce therapeutic and toxic effects, that leads us to believe that thiocyanate will have a much restricted usefulness in clinical medicine.

SUMMARY

Data are presented on fifty patients subjected to seventy-four trials with thiocyanate therapy. In forty-six of these patients the hypertension was of essential type, and in the remaining four patients it was associated with chronic diffuse glomerulonephritis. Forty-four trials were made in the outpatient clinic and thirty with the patients confined to the hospital.

Observations were made on the daily excretion rate of thiocyanate in the urine and the number of days necessary for its complete elimination after continuous medication and after a single dose in patients with essential hypertension and nephritic hypertension and in normal persons.

Toxic effects of thiocyanate were not observed in four patients with chronic diffuse glomerulonephritis, three of whom responded by a satisfactory fall in blood pressure

Therapeutic, toxic or fatal effects could not be anticipated from the amount of the drug administered

The dosage found to be most effective in lowering blood pressure and least often attended by toxic manifestations was 0.326 Gm (5 grains) given daily over a period of from fourteen to seventy-eight days

Thiocyanate was 31 per cent effective in lowering blood pressure in this series

Toxic manifestations occurred in thirteen patients, or 17 per cent of the total group studied

CINCHOPHEN HEPATITIS

AN EXPERIMENTAL STUDY

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Numerous reports in the recent medical literature refer to evidences of severe liver damage, not infrequently resulting in death, in patients given cinchophen as the chief or sole therapeutic agent. This drug, originally introduced in 1908 as a mobilizer of uric acid and advocated for the relief of gout, has come to be commonly utilized as an analgesic, particularly for the relief of pain of rheumatic type. The more common use of this drug makes a further understanding of its toxic action highly desirable.

A few references were made to toxic reactions, such as the tendency to cause urticaria or digestive disturbances,¹ early in the use of this drug, but the possibility of serious consequences was not appreciated until recently. Cabot,² in 1925, first reported a death with acute hepatic atrophy following the use of cinchophen. A report on "The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning"³ has recently been given by Beaver and Robertson. They presented a review of the literature and an analysis of the pathologic changes found in five patients who died following cinchophen therapy. They found the changes in the liver to agree with the concept of a "toxic cirrhosis."

Cinchophen has been employed for several years as an aid in roentgen studies of the gallbladder due to an increased rate of accumulation of opaque halogenated phthaleins in the bile following the administration of cinchophen. Brugsch and Horsters⁴ first called attention,

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1 Herrick, W W. A Scarletiform Rash from Atophan, *J A M A* **61** 1376 (Oct 11) 1913. Phillips, John. Skin Rashes Following the Administration of Atophan, *ibid* **61** 1040 (Sept 27) 1913.

2 Cabot, R C, and Cabot, Hugh. Case Records of the Massachusetts General Hospital, Boston *M & S J* **192** 1122, 1925.

3 Beaver, D C, and Robertson, H E. The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning, *Am J Path* **7** 237 (May) 1931.

4 Brugsch, T, and Horsters, H. Ueber die Leber als Ausscheidungsorgan und uber die Wirkung der Choleretika, insbesondere des Atophans, *Med Klin* **20** 661 (May 18) 1924.

in 1924, to the increased secretion of bile following the use of the ethyl ester of paramethylphenyl cinchoninic acid Chabrol and Maximin,⁵ utilizing animals with fistulas of the common duct, with the cystic duct tied off, reported a fivefold increase in the secretion of bile following the injection of cinchophen. The relative change in biliary constituents found following the injection of cinchophen, together with the marked increase in the flow of bile, might well be interpreted as evidencing an irritation of the hepatic parenchyma. No other agent used in their study approached the cholagogue activity of cinchophen.

EXPERIMENTAL WORK

An experimental study of the possible influence of cinchophen on the liver seemed highly desirable in view of the facts stated. The icterus index of the serum and urobilinogen of the urine were determined in four dogs and eight rabbits. These indicators of hepatic function gave values within the normal range in each instance. A section of liver was then removed under morphine analgesia and local anesthesia in order to avoid any hepatic disturbance from systemic anesthesia. These biopsy specimens were considered control material for the respective animals. Four rabbits and the four dogs were then given daily doses of cinchophen by mouth. The drug was mixed with the food given the rabbits and was administered in enteric capsules to the dogs. Thirty milligrams per kilogram of weight was considered in keeping with the therapeutic dose for man. One dog was given the therapeutic dose, two were given twice this amount, and another received five times the therapeutic dose. The rabbits were each given ten times the calculated therapeutic dose. The drug was given to the dogs for seventeen days, while the rabbits received it for forty-five days. Another section of liver was removed at the completion of the administration of cinchophen, and additional sections were removed from the dogs following a period allowed for recovery. Sections of the liver were removed from four rabbits kept under similar conditions but not given any drug, at the beginning and end of the experimental period, these sections serving as control checks on the sections from the experimental animals.

The department of pathology of the medical school prepared the sections of liver removed from all the animals. Dr. Warren C. Hunter, assistant professor of pathology, expressed the following opinion concerning the histologic appearance of the sections:

The cytological alterations in the livers of both rabbits and dogs receiving different multiples of the therapeutic dose of cinchophen were identical in kind

5 Chabrol, E., and Maximin, M. *Recherches experimentales sur les cholagogues administres per voie veineuse*, *Presse méd* **37** 666 (May 22) 1929.

but varied somewhat in degree according to the amount of drug administered. It would appear also that dogs are more susceptible to cinchophen than rabbits since the evidence of liver damage was approximately the same in rabbits that received larger amounts per kilogram weight for a period approximately three times as long as that in which the dogs received the drug.

When compared to the normal biopsy control section in individual cases, the following changes were detected in the liver for a variable distance about the central veins the cytoplasm of the hepatic cells had lost the normal finely reticular-granular structure and appeared as coarse, distinctly separated granules between which the delicate reticulum was lacking. Although at times indistinct, the cell borders were still intact and there was no actual fragmentation or autolysis. Fat stains gave negative results. The nuclei exhibited constantly some degree of chromatolysis and rather commonly contained a single, prominent nucleolus, not often encountered in control material. Mitotic activity was lacking.

The lesions in the liver sections removed from the dogs proved to be identical with those in the rabbits. In the dogs allowed a recovery period after stopping the drug it was found that with one exception (dog no 2), the damage had been recovered from. The liver of dog no 2 still manifested evidence of liver injury but no cirrhotic changes were noted.

Dog 2 had received the largest dose of cinchophen, five times the calculated therapeutic amount, which might well account for the remaining evidence of liver damage approximately one month following cessation of the administration of cinchophen. Glycogen stored in the liver has been shown to protect that organ against the toxic action of chloroform⁶. The relative resistance of the rabbits toward liver damage from cinchophen, as contrasted with that of dogs, might be explained on the basis of the relative carbohydrate content of their food.

In the majority of instances, negative results were obtained in testing for urobilinogen with undiluted urine, with urine diluted 50 per cent with water, the results were always negative. The icterus index never gave values higher than 6. Readings were obtained by means of the DuBosc colorimeter or by the standard tube technic of Farahaugh and Medes⁷. We were surprised to find the urobilinogen test and icterus index giving no indication of the change found as a routine in the liver following the administration of cinchophen.

While this work was in progress, Churchill and Van Wagoner⁸ reported on an experimental study of acute cinchophen poisoning in dogs given large (twenty-seven times the calculated therapeutic dose) amounts of cinchophen. Ulcers were found in the mucosa of the

6 Graham, E. A. The Resistance of Pups to Late Chloroform Poisoning in Its Relation to Liver Glycogen, *J. Exper. Med.* **21** 185, 1915.

7 Farahaugh, C. C., and Medes, G. A New Set of Potassium Dichromate Standards for Determination of the Icterus Index, *J. Lab. & Clin. Med.* **14** 681, 1928-1929.

8 Churchill, T. P., and Van Wagoner, F. H. Cinchophen Poisoning, *Proc. Soc. Exper. Biol. & Med.* **28** 581 (March) 1931.

stomach and lesions in the liver, which varied from "small areas of coagulation necrosis" to "complete disappearance of liver cells in small areas" The gastric and intestinal mucosa of the rabbits and of one dog, which were killed without waiting for recovery observations, were found to be without evidence of ulceration or even inflammation The difference in the doses used in the two studies may well account for the presence or absence of damage produced in the mucosa of the upper alimentary tract

CONCLUSIONS

1 Cinchophen apparently produces damage to the cells of the liver in dogs and rabbits following the administration of that drug by mouth for short periods of time

2 The degree of liver damage varies directly with the dosage of cinchophen

3 Dogs appear to be more susceptible to cinchophen toxicity than rabbits

4 The icterus index and urobilinogen test do not indicate the extent of liver damage in the dog and rabbit that is evident on histologic examination

5 The therapeutic employment of cinchophen does not seem justifiable in view of the evidences of its toxicity

ABSORPTION OF COMPOUND SOLUTION OF IODINE FROM THE GASTRO-INTESTINAL TRACT

WITH SPECIAL REFERENCE TO THE ABSORPTION OF FREE IODINE

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Although iodine had been used with beneficial results in isolated cases of exophthalmic goiter prior to 1923, the widespread use of compound solution of iodine, U S P, is the result of a paper by Plummer and Boothby¹ published in that year. Since then compound solution of iodine has been used by nearly every clinician for treatment and in the preoperative and postoperative care of patients with this disease. Plummer and Boothby¹ stated that they used liquor iodi compositus "because it is an aqueous solution of iodine (5 per cent) and potassium iodide (10 per cent) and therefore provides a large amount of iodide loosely combined with potassium."

It would appear that Plummer and Boothby¹ believed that since compound solution of iodine contains free iodine, a greater amount of iodine is available for absorption than there would be if potassium iodide were used alone. Although many papers on the clinical results of the administration of compound solution of iodine have accumulated, a careful survey of the literature has failed to reveal any experimental data on the absorption of this solution.

This study was originally begun to ascertain whether or not iodine in the form of compound solution of iodine was absorbed from the large bowel. Its scope was subsequently widened so that studies have been made of the absorption of free iodine, of iodine in compound solution of iodine, of potassium iodide and potassium iodate from the large bowel of the dog. Studies were then made of the absorption of free iodine, of iodine in compound solution of iodine and of iodide from the stomach and small intestine. It was necessary to concern ourselves with the form in which iodine is absorbed from the gastro-intestinal tract and the rate of absorption when iodine in different forms is used.

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From the Laboratory of Research Surgery, University of Pennsylvania

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1 Plummer, H S, and Boothby, W M. The Value of Iodin in Exophthalmic Goiter, Collected Papers of the Mayo Clinic and the Mayo Foundation, 1923, vol 15, p 565

METHOD

Normal healthy dogs were used in all experiments. Sodium iso-amyl-ethyl barbiturate (sodium amytal) was the anesthetic used in each instance, being administered intraperitoneally in a dosage of 50 mg per kilogram of body weight. Each experiment covered a period of two hours.

Isolation of the Colon—A midline incision was made through the skin, fasciae and linea alba. The ileocecal region was then isolated, and the ileum ligated as close to the cecum as possible with a heavy ligature. The appendix was dissected free from its mesenteric attachment for a short distance and the tip cut off. A Paul tube fitted on each end with a small piece of rubber tubing was then carefully inserted into the appendix, and care was taken that the tube extended into the colon. The tube was made secure and watertight by double ligation with heavy ligatures. A funnel was attached to the rubber tubing of the Paul tube, and the colon thoroughly cleansed with warm tap water until the water returned perfectly clear. Two purse string sutures of strong linen thread were sewed around the anus, and then a Paul tube was inserted well into the rectum. The purse strings were then tightened. The colon was again rinsed in order to ascertain whether or not any water leaked around the rectal tube. The colon was emptied by carefully forcing air through it. A clamp was then placed on the rubber tube attached to the rectal Paul tube, and the solution to be studied was allowed to run into the colon from the appendical tube at a pressure of not over 100 mm of water, until the colon was moderately distended. A clamp was then placed on the rubber tube attached to the appendical Paul tube. The wound was held together by two or more Allis forceps to conserve the body heat.

At the end of two hours the clamps were removed, and the solution was drained off by the means of air forced through the colon. The dog was killed immediately, and the entire colon, excluding the portion from the internal sphincter to the anus, was removed for the analysis of its iodine content by fusing the intestine with sodium hydroxide and sodium nitrate.

Isolation of the Small Intestine—The operation performed on the small intestine was similar to that on the colon. The portion of the intestine selected for investigation was isolated, and a Paul tube was inserted in each end. The bowel was cleansed as previously described, and the standard solution was introduced under similar precautions. The jejunum and ileum were the portions studied. The sections used were later removed and fused as previously described.

Isolation of the Stomach—When the stomach was being studied, the procedure was to ligate the duodenum about 1 inch (2.5 cm) from the pyloric sphincter. An opening was then made in the duodenum, and the rubber was attached to a Paul tube inserted through the sphincter into the stomach. Double ligatures held the tube firmly in place. A stomach tube was inserted through the esophagus, which was then ligated at the cardiac orifice to the stomach. After the stomach was thoroughly cleansed and emptied, the standard solution was introduced. Care was taken not to overdistend the viscus. On removing the solution to be studied, it was deemed sufficient to wash the stomach with approximately 1,000 cc of distilled water and analyze the washings rather than to fuse the organ and analyze the fused material.

The method employed for the determination of total iodine was that devised by Kendall,² with the exception of the slight modifications suggested by Kelly and

² Kendall, E. C. Determination of Iodine in Connection with Studies in Thyroid Activity, J Biol Chem 43 149, 1920

Husband³ The sodium bisulphite was prepared by passing sulphur dioxide through a solution containing an excess of sodium bicarbonate. Blanks were run at frequent intervals in order to determine that the reagents used were iodine-free. The determination of the amount of free iodine in the solutions introduced was accomplished by the addition of starch solution⁴ and titration with thiosulphate. All determinations were made in triplicate.

The compound solution of iodine used in the experiments on the colon was freshly prepared after the method described in the "United States Pharmacopeia." In all experiments in which this solution was used, 1 cc was diluted with 99 cc of distilled water.

The aqueous solution of free iodine was prepared by gently heating iodine crystals in distilled water until a deep brown color resulted. The solution was then filtered. In animal 864, the standard solution was made by triturating a small amount of potassium iodine with a large excess of crystalline iodine and a few drops of distilled water. The paste thus formed was then diluted with distilled water and filtered.

TABLE 1—*Absorption of a Diluted Compound Solution of Iodine from the Colon*

Dog	Weight, kg	Sex	Solution Introduced				Solution Recovered			Intestinal Wall			Total Iodine Lost	
			Volume, Cc	Total Iodine, Mg	Free Iodine, Mg	Free Iodine, per Cent	Volume, Cc per Cent	Total Iodine, Mg	Volume Change, Cc	Weight, Gm	Length, Cm	Iodine Content, Mg	Mg	Per Cent
990	11.9		110	96			79	43	31	88	35	4.4	49	51
1085	11.6		140	124	50	41	114	66	26	53	30	2.5	55	44
1087	12.7		182	156	75	43	94	62	88	66	34	2.8	92	59
1105	11.7		204	167	81	49	167	111	37	52	35	1.3	55	33
1116	13.3	♀	176	93	39	42	97	39	79	64	28	2.2	51	25
Average														48.4
Probable error														±4.6

In this study no attempt was made to make determinations of the iodine in the blood.

RESULTS

Colon—Table 1 gives the results of five experiments in which a diluted compound solution of iodine was placed in the colon. The absorption of iodine varied from 33 to 59 per cent, the average being 48.4 ± 4.6 per cent.

In these experiments I was unable, at any time, to elicit a blue color on the addition of starch solution to the fluid recovered from the colon at the completion of the experiment, this indicates that after a two-hour period in the colon no free iodine was present. The free iodine might have formed some chemical combination or have been adsorbed.

3 Kelly, F. C., and Husband, A. D. Method of Estimating Minute Quantities of Iodine in Biological Material, *Biochem J* **18** 951, 1924.

4 Treadwell, F. P., and Hall, W. T. Quantitative Analysis, New York, John Wiley & Sons, Inc., 1924, vol. 2, p. 557.

to protein, mucus or fat. In order to ascertain what became of the free iodine present in the diluted compound solution of iodine, a new series of experiments was performed.

If the free iodine were adsorbed to the fat, mucus or proteins of the intestinal tract, a pink color would have been obtained when some of the recovered solution was thoroughly shaken with chloroform or a blue color when starch was added. This was tried, but the results were negative.

In the second group of experiments (table 2, group 1), solutions containing from 98 to 100 per cent of free iodine were introduced into

TABLE 2—*Experiments Made to Ascertain What Becomes of Free Iodine Present in Diluted Compound Solution of Iodine*

Drug	Loeus	Dog	Solution Introduced			Solution Recovered			Intestinal Wall Iodine Content, Mg	Total Iodine Lost	
			Volume, Cc	Total Iodine, Mg	Free Iodine, Mg	Volume, Cc	Total Iodine, Mg			Mg	Per Cent
1 Aqueous iodine	Colon	864	129	33	35	88	21	1	14	38	
		968	126	55	55	63	19	2	34	62	
2 Potassium iodide	Colon	724	148	75		80	27	1	47	63	
		1091	198	97		111	37	1	60	62	
3 Iodate	Colon	1000	155	62		90	41	1	20	32	
4 Compound solution of iodine	Ileum	1126	64	62	26	26	16	1	45	73	
		812	40	40	18	25	13	1	26	64	
5 Aqueous iodine	Ileum	1115	160	46	46	94	14	1	31	67	
		1147	61	13	13	16	3	1	14	77	
		1148	162	50	50	121	18	1	31	62	
6 Potassium iodide	Ileum	553	80	32		34	7	1	24	74	
		513	47	22		13	3	1	18	80	
7 Compound solution of iodine	Jejunum	1126	56	54	23	34	15	1	39	72	
		812	69	68	31	21	14	2	52	76	
8 Aqueous iodine	Jejunum	968	71	31	31	23	5	1	25	81	
		1147	55	16	16	7	2	1	14	84	
		1148	123	38	38	59	10	1	27	72	
9 Potassium iodide	Jejunum	553	85	34		47	6	1	27	80	
		513	66	31		16	6	1	24	78	

the colon. Tests for starch and chloroform were performed, with negative results for the recovered solutions, indicating that the free iodine had been changed.

The addition of sufficient dilute hydrochloric acid to bring a solution, containing iodine and iodate, to a p_H of about 6.4, with starch as an indicator, will give a blue color. I have been successful in only a few instances in obtaining positive tests for the presence of both iodate and iodide in the recovered solutions. The addition of iodate and dilute hydrochloric acid to the recovered solutions, whether diluted compound solution of iodine or an aqueous solution of free iodine had been used, elicited a blue color with a starch indicator. This indicated that iodide was present.

In table 2 (group 2) are given the results of the absorption of a solution of potassium iodide from the colon, the concentration of iodine being approximately the same as that of the free iodine in the experiments in which a diluted compound solution of iodine was used. It will be noted that the absorption of iodine, in the form of potassium iodide, was higher than that found when diluted compound solution of iodine or an aqueous solution of iodine was used. However, there were considerable variations in the percentile absorption in the individual experiments.

One experiment (group 3, table 2) was performed with a solution of potassium iodate that had an iodine concentration approximately the same as that used in our other experiments, in order to ascertain the rate of absorption and to determine whether or not the iodate was reduced to the iodide. The absorption of iodine was 32 per cent. The addition of starch and dilute hydrochloric acid to the original solution failed to produce a blue color, but the addition of these substances to

TABLE 3—Iodine Content of Normal Intestinal Wall Control Experiments

	Weight, Gm	Length, Cm	Total Iodine Content
Colon	58.69	30.00	0.31
Colon	51.35	28.75	0.45
Small intestine	78.00	87.50	0.10
Small intestine	90.00	150.00	0.19

the recovered solution produced a blue color. This indicated that iodide was now present.

Similar experiments with the exception of the one performed with iodate solution were carried out on the ileum, jejunum and stomach. The results will be presented in the order of the viscus named.

Ileum—Group 4, table 2, gives the results of two experiments in which a dilute compound solution of iodine was introduced into the ileum. The absorption was 65 to 73 per cent. Tests for free iodine in the recovered solution were negative. When an aqueous solution of free iodine was placed in the ileum (group 5), the absorption was 62 to 77 per cent, and with potassium iodide alone (group 6), from 74 to 80 per cent.

Jejunum—The results of the absorption from the jejunum of diluted compound solution of iodine, an aqueous solution of iodine and a solution of potassium iodide are given in table 2, groups 7 to 9. The figures obtained in the individual experiments indicate that the amount of iodine absorbed from these solutions is practically the same.

Stomach—A series of seven experiments was performed on the stomach. These experiments were more difficult to control from the standpoint of complete emptying of the gastric washings. The con-

version of free iodine into iodide and iodate does not take place in an acid medium. The repeated washing of the stomach reduces the amount of acid in the later washings to a minimum, and under such conditions it has been found that free iodine can be changed to iodide. In this type of preparation, 18 per cent of the solution of free iodine in water was absorbed, 27 per cent of iodine was absorbed from a diluted compound solution of iodine and 31 per cent of the iodine from a solution of potassium iodide. In every instance the recovered solutions gave negative reactions for free iodine, but positive tests for iodide.

Iodine Content of Normal Intestine—Two normal colons and two portions of normal intestine were individually fused and their iodine content analyzed by Kendall's method.² This was done to serve as a control for other experiments. The total iodine content in milligrams for the normal colon (average 0.38) and normal small intestine (average 0.14), table 3, was so small as to be considered negligible, in comparison with the final results in our experiments.

Time Required for the Conversion of Free Iodine Into Iodide—That not more than two hours are required for the complete conversion of free iodine, in the concentrations used in these experiments, was indicated by the fact that negative reactions for starch and chloroform were obtained in each instance on the solutions recovered from the gastro-intestinal tract. It was thought that it would be interesting to ascertain the minimum time required for the reaction to be completed. When an aqueous solution of free iodine was introduced into 200 cm of small intestine, prepared in the usual manner, I was unable to elicit a blue color with starch four minutes after the solution had been introduced. The addition of dilute hydrochloric acid and starch gave a blue color indicating the presence of both iodide and iodate.

COMMENT

The data obtained from these experiments indicate that free iodine, when introduced into the gastro-intestinal tract, is converted into iodide. We attribute this phenomenon to an inorganic reaction.

Free iodine will combine with sodium bicarbonate in vitro as follows: $6\text{NaHCO}_3 + 3\text{I}_2 = 5\text{NaI} + \text{NaIO}_3 + 6\text{CO}_2 + 3\text{H}_2\text{O}$. This reaction can be made to take place at will, by passing iodine vapor through a saturated solution of sodium bicarbonate. Before the solution is tested with dilute hydrochloric acid and starch for the presence of iodide and iodate, the free iodine must be entirely driven off by boiling. That this reaction takes place in the range of alkalinity present in the intestinal tract seems evident.

Our experimental data indicate that free iodine is converted into iodide when instilled into the gastro-intestinal tract. If this is true,

the administration of potassium iodide in the treatment for exophthalmic goiter should be of the same value as compound solution of iodine. Neisser,⁵ Loewy and Zondek⁶ and recently Lerman and Means⁷ have shown that potassium iodide is as efficacious as compound solution of iodine in controlling the basal rate in hyperthyroidism. Lerman and Means⁷ suggested that "potassium iodide solution is preferable to Lugol's solution being equally effective and less offensive to take." Judging from these authors' clinical data and the experimental data on which this paper is based, I am in full accord with such a statement.

As previously stated, Plummer and Boothby¹ used compound solution of iodine, because it "provides a large amount of iodine loosely combined with potassium," assuming that more iodine would be present for absorption. The studies here reported do not bear out this assumption.

CONCLUSION

Studies on the rate of absorption of free iodine in aqueous solution, of a diluted compound solution of iodine and of potassium iodide and potassium iodate from the gastro-intestinal tract of the dog are reported. These studies show that the iodine is converted to iodide before it is absorbed. If these studies are applicable to the human being, they would seem to refute the assertion that compound solution of iodine is more beneficial than potassium or sodium iodide in controlling the high basal metabolism of exophthalmic goiter, since when compound solution of iodine is used, the percentage of iodine absorption is no greater than when potassium or sodium iodide is administered.

Dr C G Johnston and Dr I S Ravdin gave assistance and advice in this study.

5 Neisser, E. Ueber Jodbehandlung bei Thyreotoxikose, Berl klin Wchnschr **57** 461, 1920.

6 Loewy, A., and Zondek, H. Morbus Basedown und Jodtherapie, Deutsche med Wchnschr **47** 1387, 1921.

7 Lerman, J., and Means, J. H. Iodin in Exophthalmic Goiter. A Comparison of the Effect of Ethyl Iodid and Potassium Iodid with that of Lugol's Solution, Am J M Sc **181** 745, 1931.

IMMUNITY TO TUBERCULOSIS

RELATION OF CUTANEOUS ALLERGY AND RESISTANCE TO TUBERCULOUS INFECTION FOLLOWING VACCINATION WITH B C G

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My observations¹ that student nurses with positive reactions to the Pirquet test present greater resistance to tuberculous infection than those whose reaction is negative, suggest the importance of cutaneous allergy in relation to immunity in tuberculosis. I have also demonstrated that the subcutaneous or intracutaneous injection of B C G vaccine, in nurses presenting negative reactions to the test, is able to produce a positive reaction within a certain time. On this account I was led to believe that vaccination with B C G exercises a protective influence against tuberculous infection. These conclusions made in 1926 are the basis for the decision to vaccinate subcutaneously with B C G the student nurses in the Oslo Kommunale Sykehus who enter on their course with negative reactions to the Pirquet test. This method of vaccination has been followed systematically in this hospital since January, 1927.

Among the approximately 120 student nurses admitted annually to this hospital, nearly 50 per cent give negative reactions to the Pirquet test. During the three year course of instruction the nurses are thoroughly exposed to tuberculous infection in caring from time to time for from 300 to 400 tuberculous patients. This fact has been adequately stressed in my previous publications¹.

The conditions for intimate observation and study of the general health of these student nurses are ideal. Since tuberculous infection most often manifests its eventual malignant course for a short time after the infection, there is now sufficient reason to analyze carefully the direct results of vaccination during the past five years. What conclusions can be drawn from these experiences?

In table 1 is summarized the incidence of tuberculous diseases among the persons vaccinated with B C G strain and those not vaccinated up to

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From the Medical Division, Ullevål Kommunale, Sykehus

1 Heimbeck, J. Om tuberkuloseresistens, Norsk mag f lægevidensk 88 457, 1927. Cutireaction de Pirquet après la vaccination par B C G, Presse méd 38:1070, 1927, Immunity to Tuberculosis Arch Int Med 41:336 (March) 1928, Tuberkulose Infektion und Tuberkulose Vakzination, Ztschr f Tuberk 52 378, 1928, Tuberculous Infection, Arch Int Med 47 901 (June) 1931

July 31, 1931 It is observed that the Pirquet reaction and immunity against tuberculous infection are reciprocally related Thus there were among 454 persons with positive reactions to the Pirquet test twelve cases of tuberculosis, or 2.6 per cent, while among 253 subjects with negative reactions there were seventy-five cases of tuberculosis, or 29.6 per cent The annual curves have been uniform with these figures

It is evident, however, that the results for each year have not been uniform among the vaccinated persons These subjects seem to fall into

TABLE 1—*Relation of Cutaneous Allergy and the Incidence of Tuberculous Infection Among Student Nurses During Their Hospital Service*

Year	Number of Student Nurses	Pirquet Test	Vaccinated with BCG	Number Taken Ill with Tuberculosis									Total
				During Half Year								Later Half Year	
				1	2	3	4	5	6	7	8		
1924	58	Positive	—	—	—	—	—	—	—	—	—	1	1
	51	Negative	—	5	4	1	4	1	1	1	—	—	17
1925	42	Positive	—	—	—	—	1	—	—	—	—	—	1
	72	Negative	—	8	4	6	2	—	1	—	—	—	21
1926	52	Positive	—	1	—	—	—	—	—	—	—	—	1
	62	Negative	—	8	4	2	—	2	—	—	—	—	16
1927	64	Positive	—	—	1	1	—	—	—	—	—	—	2
	12	Negative	—	4	—	1	—	—	—	—	—	—	5
	45	—	45	—	—	—	—	1	—	—	—	—	1
1928	65	Positive	—	1	—	2	—	1	—	—	—	—	4
	19	Negative	—	5	4	1	—	—	1	—	—	—	11
	40	—	40	1	—	1	—	1	—	—	—	—	2
1929	61	Positive	—	2	—	—	—	1	—	—	—	—	3
	4	Negative	—	—	—	—	—	—	—	—	—	—	0
	52	—	52	—	1	1	—	—	—	—	—	—	2
1930	58	Positive	—	—	—	—	—	—	—	—	—	—	0
	7	Negative	—	—	3	—	—	—	—	—	—	—	4
	43	—	43	—	8	1	1	—	—	—	—	—	10
1931	54	Positive	—	—	—	—	—	—	—	—	—	—	0
	26	Negative	—	1	—	—	—	—	—	—	—	—	1
	27	—	27	3	1	—	—	—	—	—	—	—	4

Summary Positive Pirquet tests 454 tuberculosis 12 (2.6 per cent)
 Negative Pirquet tests 253, tuberculosis 75 (29.6 per cent)
 Vaccinated with BCG 207, tuberculosis 20 (9.6 per cent)

two groups First, those vaccinated during the years 1927, 1928 and 1929, and second, those vaccinated during 1930 and 1931 In the first group, six cases of tuberculosis occurred among 137 vaccinated persons The period of observation extended from two years to four years and a half In the second group, there were fourteen cases of tuberculosis among seventy vaccinated persons, the longest period of observation being one year and a half These results require a closer scrutiny in order to evaluate the effects of vaccination and of other attendant circumstances

I have previously called attention to the great variableness in local and allergic reactions following vaccination with BCG While in cer-

tain persons local reactions develop at the site of inoculation, others fail to react, and in some the reaction to the Pirquet test becomes positive following vaccination, while in others it remains negative. These variable results are shown in table 2.

A total of 207 vaccinations have been made. Forty of these must be eliminated (groups 7 and 8) from the final appraisal because of inadequate controls, and the last three, performed on July 10, 1931, must also be eliminated because the general incubation time for B C G has not yet expired at the time of this report. This leaves 164 vaccinations for consideration in the present study. When the subjects are grouped according to their reactions to the Pirquet test following vaccination and

TABLE 2—*Local and Allergic Reactions Following Vaccination with BCG*

Vaccinations		Grouping of Reactions							Course Discon- tinued	Ill
		P+,* Inf 2 Mm or More	P+, Inf Under 2 Mm	P+ and Local Inf	P+ and Local Abscess	P- and Local Inf	P- for 6 Months or Until Infection	Not Con- trolled First 6 Months		
Year	Num- ber	1	2	3	4	5	6	7	8	
1927	45	33	6	8 1	2		1	4	1	1
1928	40	12	6 1	6		2	10 1	2 1	2	3
1929	52	11	3 1	5	2	1†	2 1	24	4	2
1930	43	5			1		36 10§		1	10
1931	27†	1	1	1	11	3‡ 1	5 3		2	4

* In this and the following table, P+ represents positive Pirquet reaction, P-, negative Pirquet reaction, Inf indicates infiltration.

† The last three vaccinated persons (July 10, 1931) are not included.

‡ Infiltration not larger than a pea.

§ One of these subjects died of tuberculous meningitis.

before they were exposed to tuberculous patients, the following results are obtained. In 104 persons the Pirquet test became positive (groups 1, 2, 3 and 4) and in sixty persons the reaction remained negative (groups 5 and 6). Among the 104 subjects with positive reactions to the Pirquet test, tuberculosis developed in three or 3 per cent, while among the sixty with negative reactions, tuberculosis developed in sixteen, or 26.6 per cent. These results are not surprising according to the present interpretation of the Pirquet reaction. This criterion furnished the chief reason for the systematic vaccination with B C G of persons with negative reactions to the Pirquet test, since it appeared that these persons are exquisitely susceptible to tuberculous infection. Subsequently, the course adopted by my associates and me has been to produce a positive reaction to the Pirquet test by means of the subcutaneous injection of the B C G vaccine.

The significance of the Pirquet test is further enhanced when the persons with doubtful reactions (group 2) who present an area of inhibition measuring less than 2 mm in diameter are eliminated. Among these subjects with doubtful reactions sixteen persons are listed, and in two of these tuberculosis developed. This group is sharply separated from the groups 1, 3 and 4, which present distinct reactions to the Pirquet test, in which the area of infiltration is in excess of 2 mm in diameter. Only a single case of tuberculosis occurred among the eighty-eight persons with distinctly positive reactions to the Pirquet test. So group 2 stands between the positive and the negative groups (groups 5 and 6) which presented sixteen cases of tuberculosis among sixty persons.

It is quite apparent, therefore, that it is the vaccination with B C G, that elicits the positive reactions to the Pirquet test which really produces an effective resistance against tuberculous infection. Should cutaneous allergy fail to be developed following the vaccination with B C G there is good reason to conclude that no effective vaccination has been produced against tuberculous infection. The many divergent results reported following vaccination with B C G must be attributed to the failure of the vaccine to call forth cutaneous allergy. While certain persons have become allergized and immunized following vaccination with B C G, in others it has not been effective. And since only occasional studies have been made of the reaction to tuberculin of persons vaccinated with B C G, one is not in a position to know positively the allergizing effect of the vaccination, that is, the number of persons successfully vaccinated.

Table 2 shows clearly the variableness of the local and allergic manifestations following vaccination with B C G. Certain injections elicit local abscess and allergy, others produce no reactions, while still others result in intermediary manifestations.

During the year 1927, a dose of 0.05 mg. of B C G was administered to each of forty-five persons. Ten had local reactions, of which two were abscesses, while thirty-five showed no local reaction, in one the reaction remained entirely negative, locally and allergically, following vaccination.

These variations may be conditioned by two factors: (1) the person treated with B C G and (2) the injected vaccine. The ability to react to B C G vaccine must doubtless show wide variations. Although they are treated on the same day and with the identical bacterial emulsion and dosage the effects are most variable in a group of persons. For example, on Jan. 11, 1928, nineteen student nurses with negative reactions to the Pirquet test were vaccinated with 0.05 mg. of B C G. One of these nurses was eliminated because of lack of control. In the

remaining group of eighteen, local infiltration developed in five, while in the other thirteen the reaction remained negative locally. When tested with tuberculin, ten gave positive reactions to the Pirquet test following vaccination (table 3, groups 1, 2 and 3), and in eight the Pirquet test remained negative (groups 5 and 6). Similar variations have been repeatedly observed and seem quite natural.

Concerning the second factor, the vaccine employed, a certain variableness is encountered here also, which is best illustrated by the following observations (table 3). On Feb. 25 and 28, 1927, five student nurses were given injections of 0.05 mg. One subject should be eliminated because of lack of control. In the remaining four the Pirquet test became positive, and in one an abscess developed locally. On July 14, of the same year, twenty-one student nurses received the

TABLE 3—*The Variability of the Effectiveness of Vaccination with BCG*

Date, Number and Dose of Vaccine Group	Grouping of Reactions							Course Discon- tinued
	P+, Inf 2 Mm or More	P+, Inf Under 2 Mm	P+ and Local Inf	P+ and Local Abscess	P- and Local Inf	P- for 6 Months or Until Infection	Not Con- trolled First 6 Months	
	1	2	3	4	5	6	7	
2/25 28/27 5 vaccinated, 0.05 mg	3			1			1	
7/14/27 21 vaccinated, 0.05 mg	11	1	1			1	3	1
1/11/28 19 vaccinated, 0.05 mg	4	2	4		1	7	1	
6/14/29 10 vaccinated, 0.025 mg	1	2	5	1		1		

same dose (0.05 mg) of BCG. Four of these should be eliminated. Among the remaining seventeen nurses vaccinated a local infiltration developed in one, the Pirquet test became positive in fifteen and there was a doubtful reaction to tuberculin in one, and in one the reaction to the Pirquet test remained negative. The effectiveness of these two vaccinations was accordingly practically uniform. But the results of the vaccination on Jan. 11, 1928, were not so, as was mentioned. Among the nineteen nurses vaccinated local infiltration developed in five, but still the reaction remained negative in eight, and in two the reaction to the Pirquet test was doubtful. On June 14, 1929, the vaccine was again more effective. On that day only 0.025 mg of BCG was injected into ten student nurses. In five local infiltration developed, in one case a local abscess, in seven the reaction to the Pirquet test became positive, while two reactions were doubtful (group 2), and only one remained negative.

A comparison of the results compiled during the entire year of 1929 with those obtained for 1930 also discloses a marked variability in the

effects of vaccination with B C G Fifty-two persons were vaccinated during 1929, fifty of these received 0.025 mg and two received 0.03 mg of B C G Table 2 shows that among the twenty-four who were adequately controlled, in eighteen the Pirquet test became positive, in seven local reactions developed, and in two tuberculosis developed as a result of a later infection During 1930, forty-three persons were vaccinated Of these, twenty-eight received 0.03 mg, fourteen received 0.025 mg and one was given 0.04 mg—in general, greater doses than in 1929 But among the forty-two persons vaccinated who were exactly controlled, in only one did a local reaction (an abscess) develop, and in only six did the Pirquet test become positive, while in thirty-six it remained negative In ten members of this group tuberculosis developed when the nurses later were exposed to infection

The B C G vaccine employed in these different groups appears, therefore, to yield a variable local and allergic effect These different effects of the B C G vaccinations are remarkable

It is possible that the age of the B C G vaccine may play an important rôle This seems to be suggested in the following observation On June 11, 1930, ten student nurses were given injections of 0.03 mg of B C G Since this culture had grown poorly, it became necessary to leave it in an incubator for forty-five days before sufficient growth had taken place for it to be used as a vaccine Among the ten nurses vaccinated with this lot, none showed local irritation, and in all of them the Pirquet test remained negative as before vaccination In five of these persons tuberculosis has since developed The vaccine seems, therefore, to have failed to produce any immunizing effect It is only in this instance that the age or dysgonic property of the B C G strain seems to have been responsible for its ineffectiveness as a vaccine The production of vaccine has otherwise always been according to the directions of Calmette But the possibility of uncontrollable variations in the mediums employed for the cultivation of B C G and in the production of the vaccine must also be taken into consideration Whatever is the real explanation of these divergent results, one thing is certain, namely, that the B C G vaccine is not constant in eliciting local and allergic effects The B C G virus cannot be considered as a fixed virus in an absolute sense, i e., also in its immunizing properties, although the strain remains avirulent It is imperative that the strain should produce cutaneous allergy in order to insure against tuberculous infection A positive reaction to the Pirquet test, or similar tuberculin tests, should be elicited following subcutaneous vaccination with B C G This remains a potent criterion of the fact that the vaccinated person is immunized against tuberculous infection

CONCLUSIONS

The susceptibility to tuberculous infection among student nurses with negative reactions to the Pirquet test who are exposed to tuberculous patients is excessively high (29.6 per cent), in contrast with a relatively high resistance to tuberculous infection among student nurses with a positive reaction to the Pirquet test (2.6 per cent)

Subcutaneous injection of the B C G vaccine is capable of converting a negative reaction to the Pirquet test to a positive reaction, with subsequent marked increase in resistance to tuberculous infection

The absence of a positive reaction to the Pirquet test following vaccination with B C G must be considered as an indication of inadequate vaccination and of the fact that the vaccinated person's liability to tuberculous infection has remained practically unaltered, and revaccination should be done

PROLONGED USE OF MASSIVE DOSES OF UREA IN CARDIAC DROPSY

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This report presents some of our results of the prolonged use of large amounts of urea in cases of cardiac dropsy. We shall emphasize, among other matters, chiefly three points, first, that the diuretic properties of this drug do not weaken during months and several years of practically uninterrupted use, second, that there follow no demonstrable deleterious effects on the patient, more specifically, the renal structures remain unaltered and their function unimpaired, and third, that urea acts, alone or in combination with other agents, in selected cases, as an excellent prophylactic in preventing the reaccumulation of edema. Of the many patients in our wards who were subjected to treatment with urea, we are reporting at this time the cases of five in full. These cases will illustrate the methods and results.

METHODS

Nearly all the patients in this study have been at the Montefiore Hospital for many months or several years, some have had several previous admissions. The majority, on admission, presented signs of advanced congestive heart failure with marked anasarca, they suffered from either chronic rheumatic or arteriosclerotic and hypertensive cardiac disease, but all but one were free from renal complications.

The type of diet given the patients varied. Some took the regular house diet, containing at least from 5 to 6 Gm of sodium chloride per day, others took a salt-poor diet, containing about 2 or 3 Gm of sodium chloride. The patients lived sometimes on one and sometimes on the other diet over various periods. Several received, in addition, digitalis, mersalyl or other diuretics. These details are noted elsewhere.

As a rule, except during the first few days immediately after admission, no attempts were made to limit the intake of fluid. There is no

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doubt that large doses of urea greatly increase the patient's thirst, and he proceeds to drink much larger volumes of water. It proved, however, impracticable to limit the patients' intake of water in a large ward service, because surreptitiously they drink water copiously. More reliable guides to the patient's progress with regard to loss or gain in edema were first and most important, his body weight, which was particularly valuable since the caloric intake was ample (at least 2,000 calories per day) to prevent a loss in flesh, and second, the measurement of the daily urinary output,¹ which was not always accurate, as already mentioned, but which was valuable, nevertheless, as a reflection of how the normal channels of excretion were working.

The doses of urea varied between 10 and 25 Gm, two or three times a day in 40 per cent water solution. Whenever possible, at the beginning of treatment the patients received about 18 Gm three times a day. It was seldom necessary to give more than this amount, although in some cases as much as 27 Gm three times a day was administered. After satisfactory diuresis, the drug was gradually reduced, the patients receiving 15 or even 12 Gm three times a day, and in some instances the patient remained on a 12 Gm dose twice daily, especially when the drug was employed to function as a "chronic" prophylactic measure to prevent the reaccumulation of edema.

As a general rule, the patients took the drug without remonstrance, although its taste is very unpleasant. We administered it as a 40 per cent² aqueous solution, adding no sugar. In private practice we have added the juice of a pressed lemon, or else we have used as a vehicle from 100 to 200 cc of beer or uncooked tomato juice. Recently we have tried using fresh pineapple juice or raspberry syrup, mixing from 50 to 90 cc of syrup with an equal quantity of water as a diluent for each single dose of urea. The syrups seem to be agreeable vehicles. There were seldom any untoward effects, such as nausea, heart burn

1 There are, of course, important factors in the total loss of fluid, as exemplified by the extrarenal output of water, such as "insensible perspiration," but these were not studied by us. For references see Veil, W. H. *Deutsches Arch f klin Med* **119** 376, 1916; Benedict, F. G., and Root, H. F. *Insensible Perspiration Its Relation to Human Physiology and Pathology*, *Arch Int Med* **38** 1 (July) 1926.

2 Only recently our attention was directed to the fact that patients in the hospital were receiving their urea in a 40 per cent solution and not in a 50 per cent solution as charted. This raised the doubt in our minds that, perhaps, the doses taken by the patients studied in this report may have been actually one-fifth less than we had believed. Although we think that our patients may have taken the full amounts, for example, from 70 to 80 Gm daily, we deemed it more accurate and safer to base our results on a corrected calculation. Accordingly, all figures noted in the text represent four fifths of the amount charted in the history records.

or other gastric symptoms. We tried producing a chocolate or gelatin covered tablet, but without success, because urea cannot be concentrated into tablets of small bulk for adequate dosage.

REPORT OF CASES

CASE 1—R. Z., a woman, was admitted to the Montefiore Hospital six times, from 1923 to 1927, suffering from chronic rheumatic cardiovalvular disease. On Jan. 8, 1929, at the time of her last admission, she was 28 years old, she again showed congestive failure, auricular flutter and partial heart block, which changed to auricular fibrillation (she was taking digitalis). Toward the end of August of that year she grew worse, although she was receiving a maintenance dose of digitalis almost daily, on November 3, the therapy was supplemented with urea, from 24 to 36 Gm. daily. From September 1 until November 1 her weight was practically unchanged (from 133½ to 135 pounds [60.5 to 61.2 Kg.]). When she was given urea, however, for the next forty-five days, the weight fell to 122½

TABLE 1—*Treatment and Results in Case 1*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea		Weight, Pounds	Other Diuretics
		1929			
0	133½	61	Sept. 1 to Nov. 1	135	Digitalis
24 to 36		45	Nov. 3 to Dec. 18	122½	Digitalis
		1930			
56		46	to Feb. 3	120	Digitalis
0		57	to April 1	125	Digitalis
36 (occurs 56)		52	to June 22	121	Digitalis
56		70	to Aug. 31	114 to 117½	Digitalis

pounds (55.5 Kg.) and the clinical condition improved. The dose of urea was raised to 56 Gm. through the next forty-six days, the weight touching 120 pounds (54.4 Kg.). The following fifty-seven days the patient took no urea, but she remained restored in cardiac efficiency and her weight did not rise above 125 pounds (56.7 Kg.). The next eighty-two days she took mostly 36 Gm. a day, the weight was 121 pounds (54.9 Kg.). The final seventy days of this record she took 56 Gm. a day, and her weight fell to between 114 and 117½ pounds (51.7 and 53.3 Kg.).

This case demonstrates that digitalis alone was not able to restore the patient's cardiac efficiency and rid her of her signs of congestive failure, but that when urea, in doses of from 24 to 36 Gm. a day, was added, the desired result was achieved. Urea seemed very helpful in this case, although its administration was irregular because the patient refused the drug on several occasions. A point worthy of emphasis is that she finally required no other diuretics. Her renal function was good. She had an output of about 567 mg. of sodium chloride daily. The figures for the blood urea nitrogen were 24.2 mg. per hundred cubic centimeters on Aug. 5, 1930, after urea had been withheld for the ten preceding days, and from 36.8 to 49 mg., while patient was receiving urea, thirteen and one-half months, and there was no disturbance in the urinary concentration power. She remained edema-free, although her cardiac reserve was very poor. She finally died of congestive heart failure, on July 1, 1931.

CASE 2—H R, a man, aged 56, came to the Montefiore Hospital on Dec 28, 1928. The diagnosis was degenerative cardiovascular disease, auricular fibrillation and congestive heart failure. He received digitalis practically daily until May 11, one hundred and twenty-eight days, during the initial nineteen days of which he took 56 Gm of urea, his weight fell from 165½ to 148½ pounds (75 to 67.3 Kg). The following twenty days, with 36 Gm a day, the weight went still lower (134½ pounds [61 Kg]), this figure was maintained over the next twenty-three days, with 56 Gm daily. Urea was withheld for the next thirty-five days, and the weight rose to 141½ pounds (62 Kg) and then dropped slightly (138½ pounds [62.8 Kg]) with 56 Gm daily until thirty-one days later, when the patient was discharged (May 11, 1929).

The patient returned the following year, on March 11, 1930, and again showed extreme heart failure with anasarca. This time he received no digitalis. His weight was 146 pounds (66.2 Kg) on admission. During the first one hundred and fifty-six days he received 36 Gm of urea daily and no mersalyl. His weight

TABLE 2—Treatment and Results in Case 2

Daily Gm of Urea	Admission Weight, Pounds	Days on Urea	Weight, Pounds	Digitalis	Mersalyl	Comment
56	166½	19 1929 Jan 3 to Jan 22	148½	2.4 cc daily		
36	20	to Feb 11	134½	2.4 cc daily		Improved Feb 21
36	23	to Mar 6	134¼	2.4 cc daily		
0	37	to Apr 10	141½	2.4 cc daily		
56	31	to May 11	138½	2.4 cc daily		
36	146	156 1930 Mar 11 to Aug 14	137	0		In July no congestive signs
0	84	to Nov 6	143	0	Nov 7, 2 cc	
36	51	to Dec 27	135	0	Dec 13, 2 cc	
		to 140				
36	141	13 1931 Jan 1 to Jan 13	142	0		Jan 21, 2 cc
0	9	to Jan 22		0		
36	9	to Feb 1		0		
0	17	to Feb 17	152	0		
6	11	to Feb 28	142	0		

soon reached and remained at about 137 pounds (62.1 Kg), and very early he exhibited marked clinical improvement, which he maintained. The following eighty-four days he took no urea, his weight stayed at about 143 pounds (64.9 Kg), and he required but one injection of mersalyl. The final fifty-one days of this period he received 56 Gm of urea daily and but one injection of mersalyl, and the weight varied from 135 to 140 pounds (61.2 to 63.5 Kg). On December 27, he was discharged very much restored in cardiac efficiency and edema-free. This period, as well as the next period, represents a contrast interval wherein the patient took no digitalis, and urea was the mainstay of treatment.

Beginning Jan 31, 1931, for thirteen days, the patient was given 36 Gm of urea. The following nine days urea was withheld, but he received 2 cc of mersalyl. The next nine days he took 56 Gm of urea daily and again stopped for the next seventeen days so that by February 17, his weight had risen to 152 pounds (68.9 Kg) as against 142 pounds (64.4 Kg) on January 31. Fifty-six grams of urea daily reduced the weight to 142 pounds within eleven days.

It will thus be seen that in the third episode, reduction in the quantity of urea led to an increase in weight and to the appearance of mild signs of heart failure, and that this condition yielded rapidly to an adequate intake of urea. No digitalis was employed, and only one dose of mersalyl was given at the very beginning of this period.

The daily urinary output of salt of this patient was good, about 55 Gm, and covered his intake. On Aug 1, 1930, his blood urea was 174 mg per hundred cubic centimeters, urea having been stopped for three days, it was 26 mg after he had been taking urea for ten and one-half months. The range of the specific gravity of the urine was normal. The renal function remained undisturbed.

CASE 3—When H. L., a man, aged 39, with hypertensive heart disease, entered the hospital on March 6, 1929, he had extreme heart failure and was water-logged. His auricles were not fibrillating. He was given digitalis daily, a dose of mersalyl intravenously on one occasion and thereafter 56 Gm of urea daily. Within twenty-four days his weight declined from 164 to 147 pounds (74.4 to 66.7 Kg), and his clinical condition improved markedly. During the next five hundred and eighty-two days he took 56 Gm of urea daily and required in all but five injections of mersalyl (2 cc each), widely spaced. The last months he took no digitalis. His output of salt in the urine was good, a concentration test of the urine showed normal renal function. On Aug 1, 1930, his blood urea nitrogen was 186 mg per hundred cubic centimeters of blood, three days after urea was discontinued, it varied from 30.1 to 36.6 mg after twenty-three and one-half months of urea therapy. The elimination of urea in the urine was normal, about 4 per cent. During all this time the patient was practically edema-free and restored considerably in cardiac efficiency.

TABLE 3—*Treatment and Results in Case 3*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea	Weight, Pounds	Mersalyl (2 Cc)	Digitalis	Comment
56	164	1929 24 March 15 to April 8	147	1929 March 21	2 cc daily	
56		582 to Nov 1, 1930	145	1930 Jan 30, July 8, Aug 6, Sept 15, Oct 24	Daily up to Dec 1, 1929, daily from Aug 14 to Sept 30	Weight, 149½ pounds
		606 days				

This record also illustrates the futility of giving mersalyl when a residual edema-free weight is well established, thus, on Jan 31, 1930, the patient's weight was 147¾ pounds (67 Kg), and although he was not edematous, he received 2 cc of mersalyl. The next day the weight stayed unchanged, and the following day it was 146 pounds (66.2 Kg). A similar result was observed on July 8, 1930, when the weight was 145 pounds (65.8 Kg), 2 cc of mersalyl reduced the weight to 142 pounds (64.4 Kg) the next day, and on the following day it was 143 pounds (64.9 Kg).

CASE 4—When L. R., a man, aged 54, first appeared at the Montefiore Hospital on Sept 17, 1927, he was known to have arteriosclerotic cardiovascular disease with hypertension and marked heart failure. Ten months later he went home much improved. On April 4, 1929, he returned, his heart failure was extreme. The blood pressure was 166 systolic and 90 diastolic, and there was pulsus alternans, electrocardiographic tracings disclosed premature ventricular beats but no auricular fibrillation. He received no digitalis, but was given during the initial twenty-six days four doses of mersalyl (2 cc each) and 56 Gm of urea daily. His weight fell from 175½ to 138 pounds (79.6 Kg to 62.6 Kg), and the clinical amelioration was striking. For the greater part of the next one hundred and eighty-four days he took 24 Gm of urea daily, occasionally 36 Gm, and he required but two widely

spaced injections of mersalyl, the weight stayed at about 135 pounds (61.2 Kg), and he was edema-free. An increase of urea to 56 Gm daily for the following one hundred and eighty-one days lowered his weight to 127 pounds (57.6 Kg), and he required but one injection of mersalyl during this time. For the next one hundred and twenty-two days, the daily dose of urea was 36 Gm, occasionally 56 Gm, but the patient required mersalyl somewhat more frequently, and his weight climbed to 138 pounds (62.6 Kg), and continued to range between 132 and 140 pounds (59.9 and 63.5 Kg) during the next two hundred and seventeen days, when he took 56 Gm of urea daily.

This patient thus took large doses of urea practically uninterruptedly over seven hundred and thirty days. On Aug. 13, 1930, after having taken urea for more than one year, the blood urea nitrogen was only 15 mg per hundred cubic centimeters, urea having been stopped for two days, after taking urea for twenty-one and one-half months, the blood urea nitrogen was 29.1 mg. The daily urinary

TABLE 4—*Treatment and Results in Case 4*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea		Weight, Pounds	Mersalyl
56	175½	26	1929	138	April 7, 10, 19, 24
36 (mostly 24)		184	April 4 to May 1 to Nov 1	135	August 12, October 26
56		116	1930	127	December 7
56		65		127	0
36 (occas 56)		31		123	May 23, 31
36		60		123	July 8, 9, 27
36		31		138	August 4, 26
56		217	1931		None for 6 months
		—			September 3, 12
		730 days			October 9, 18, 27
					November 4, 11, 14, 21, 25, 29
					December 9, 13, 19, 23, 29
					January 24, 31
					February 23

output of sodium chloride was about 5 Gm, and just about covered the intake. The specific gravity of the urine showed no fixation or limitation in range. The renal function, therefore, was good. The weight reached an early equilibrium of about 135 pounds (61.2 Kg), and never returned to the excessively high figures (175½) noted in April, 1929. There were times when the patient showed some anasarca, but it never reached the extent that it did on his last admission, this yielded to increased doses of urea, to mersalyl or to both drugs combined. For months urea was the *only* medicament, and the patient continued to be edema-free and restored in cardiac efficiency.

Case 5—J. R.,³ a man, aged 49, came to the Montefiore Hospital on March 12, 1927. His weight was 145 pounds (65.8 Kg). He had had recurrent attacks of congestive heart failure, and his signs were advanced and unrelieved on admission. The clinical diagnosis was generalized arteriosclerosis, hypertension and associated myocardial damage and marked congestive heart failure with no auricular fibrillation.

³ This case, as well as case 4, was reported at the New York Bronx County Medical Society by Dr. L. Tarr in June, 1929, as showing a good response to the continued use of urea up to that time.

The heart failure was progressive, large quantities of edema fluid collecting in the abdomen and thorax. The first six months he took digitalis almost daily, and the initial twenty-nine days of this period no urea was given. The next one hundred and eight days urea was added, in doses of from 48 to 24 Gm daily, but, thereafter, for one hundred and forty-two days, he again took no urea. During the two hundred and seventy-nine days, he required several abdominal and thoracic paracenteses, and these procedures, together with several injections of mersalyl, brought the weight down to 157 pounds (72.1 Kg), which had previously mounted to 181½ pounds (82.3 Kg). Many and various other diuretics were also tried during this period, but with little success, the cardiac function remained poor, and the anasarca, as indicated by the huge weight, was unrelieved except by the mechanical withdrawal of collected fluid. For one hundred and fifty-two days urea was then withheld, and his condition showed very little improvement. When urea

TABLE 5—*Treatment and Results in Case 5*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea	Weight, Pounds	Mersalyl (2 Cc)	Digitalis
0	145	29 1927 Mar 12 to Apr 12			1 cc daily
48 to 24		108 to July 29	167 (181½)	Aug 8 Oct 21, 24, 28 Nov 2, 6, 12, 16	1 cc daily 1 cc daily 1 cc daily
0		142 to Dec 18	157	Dec 28	Sept 12, stopped
56 or more		227 1928 to Aug 2	152, 164, 169	Feb 17	
0		152 1929 to June 1		Nov 3, Dec 25	
56		322 to Nov 20	148	Jan 1, Feb 18 Mar 29, Aug 16, Sept 3	
56 or more		410 Nov 24, 1929 to Jan 7, 1931	147-150	1929 Dec 13, 20, 29 1930 Jan 21, 30 Mar 6, 26 Dec 9, 16	
Jan 10 1931 ceased		1,067 days on urea 1,390 days in hospital			

was resumed, 56 Gm daily, over the next three hundred and twenty-two days with very infrequent injections of mersalyl, the weight was reduced to 148 pounds, and he became unmistakably improved. Practically the same dose of urea was administered daily during the remainder of his life, four hundred and ten days, and he remained stabilized in weight, from 148 to 150 pounds (67.1 to 68 Kg), requiring mersalyl at very rare intervals, if at all. Digitalis was not employed after the early six months' trial.

The patient's improvement, especially in the latter half of the course, was marked while he was taking urea, supplemented by mersalyl. Over many consecutive months urea alone was employed, and during the latter half of his stay in the hospital, while on urea therapy, he required no further paracenteses. He was in the habit of drinking large amounts of water, but he eliminated large quantities of urine (about 3,200 cc daily). His chloride output was 2.06 Gm daily over a period of many days, an amount slightly less than his intake. There were times when he gained in weight gradually, although he was taking urea, but during this period of slow gain in weight he did not require mersalyl frequently. When urea was discontinued for a short time, his weight increased at a far greater rate and his condition called for mersalyl more frequently. The renal function showed

some alteration, i. e., the range of the specific gravity became contracted (from 1 010 to 1 015), on several occasions, the blood urea nitrogen, the drug having been stopped in a test period, remained high. At autopsy the clinical diagnosis was confirmed, and arteriosclerotic changes were found in the kidneys to explain the disturbance in renal function.

THE DIURETIC VALUE OF UREA WHEN GIVEN OVER LONG PERIODS IN LARGE QUANTITIES

The use of urea as a diuretic is not new. As early as 1892, Friedrich⁴ had employed it in comparatively small doses (from 2 to 14 Gm daily) in cases of cardiac edema and in cases of ascites associated with cirrhosis of the liver. Klemperer⁵ in 1896 also successfully employed it in cases of hepatic ascites using slightly larger doses (from 10 to 20 Gm). Strauss⁶ in 1896 and again in 1921 emphasized the importance of urea as a diuretic. Feilchenfeld⁷ in 1918 obtained excellent results, giving as much as 100 Gm daily in cases of edema with normal renal function. Volhard⁸ in 1918 used large doses of from 40 to 60 Gm of urea per day in the treatment of patients with renal diseases, he obtained excellent results in cases of nephrosis. In 1921, McLean⁹ included urea in large daily doses in his list of useful diuretics for renal edema, especially for that of nephrotic origin. Crawford and McIntosh¹⁰ in 1923 gave the drug, in amounts up to 60 Gm daily, to eight edematous patients, and seven of them became completely edema-free. King¹¹ in 1927 reported on the use of urea and diets high in protein for patients with edema, his results varied in relation to the rate of elimination of urea and renal impairment. Goldring¹² in 1929 attempted to use urea for four patients with edema, but in all of them gastric disturbances developed and the administration of the drug had to be stopped. Volhard,¹³ in a discussion on the treatment for edema,

4 Friedrich, W. Eine Abhandlung über die diuretische Wirkung des Harnstoffs, *Magyar orvosi arch* **1** 400, 1892.

5 Klemperer, G. *Berl klin Wchnschr* **33** 6, 1896. Klemperer, G., and Dunner, L. *Behandlung der Nierenkrankheiten, Therap d Gegenw* **60** 57, 1919.

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10 Crawford, J. H., and McIntosh, J. F. *The Use of Urea as a Diuretic in Advanced Heart Failure, Arch Int Med* **36** 530 (Oct) 1925.

11 King, S. E. *M Clin North America* **10** 963 (Jan) 1927.

12 Goldring, W. *Edema in Congestive Heart Failure, Arch Int Med* **44** 465 (Oct) 1929.

13 Volhard, Franz, in von Bergmann, G., and Staehelin, R. *Handbuch der inneren Medizin*, ed 2, Berlin, Julius Springer, 1931, vol 6, pt 1, p 355.

stated that he had given urea in large doses for many weeks. He quoted a case of Strauss', in which the patient took 12 Kg. of urea during six months. It is therefore apparent that in the hands of a number of workers good and even excellent diuresis was secured when urea was given in adequate amounts. The workers all seem in agreement that urea is absorbed quickly, promptly raising its concentration in the blood, and is rapidly excreted, transporting with it large amounts of fluids to the kidneys, and that all this takes place without provoking, at least in normal cases, any toxic or harmful effect. There are, however, few, if any, similar observations on the very prolonged administration of urea in massive doses.

Our study, therefore, was undertaken to ascertain whether the well functioning kidney, as in our patients with cardiovascular disease, retained its ability to rid the body of large quantities of fluid in the face of continued and repeated daily demands on it when urea is administered in large amounts over many months or years. The duration of its use in some of our cases extended over several years, a period considerably longer than that hitherto reported in the literature.

Diuretic Effect of Urea—Unlike the distribution of sodium chloride in the body with its predilection for storing chiefly in the skin whence it is called on as needed, urea reaches the blood and all organs in practically equal concentration (Schoendorff¹⁴ and Marshall and Davis¹⁵). As there is no special depot for urea, it is apt after large doses to accumulate in the blood stream in high concentration, disappearing as the drug is stopped. This high concentration of blood is a material factor in urea diuresis.

While we have reported the cases of five patients who showed beneficial results over long periods of time, there are a number who failed to show this response. The factors limiting the effectiveness of urea diuresis are being investigated at present.¹⁶ In some patients in whom the diuretic response at the beginning of urea therapy was negligible, we witnessed good diuresis at a later date under seemingly identical conditions (case 5). Furthermore, the dose for optimum and maximum diuresis was not constant. Generally, the best and most prolonged diuresis followed from the daily ingestion of 56 Gm. divided into three equal portions. When small doses were given, edema reappeared slowly and steadily, and the dose had to be raised to 36 or even 56 Gm. daily.

Various other diuretics were also employed, either in combination with or as an alternative to urea. These we may classify, for practical

14 Schoendorff, cited by Loeb, E. *Edema, Med Monog* 8 77, 1923

15 Marshall and Davis. *J Biol Chem* 18 53, 1914. Weiss and Vaughan. *J Lab & Clin Med* 7 229, 1921

16 Future publication by Dr. L. Tarr

purposes, into several groups, their action is not identical and often unknown, and they possess individual differences and indications for use. In the first group we place urea. The second consists of acid and base-forming drugs: ammonium chloride, ammonium nitrate, monobasic sodium phosphate, alkalis, like soda bicarbonate in large amounts, or potassium citrate. The third group comprises metal preparations: merbaphen and mersalyl, mercurial products and bismuth salts. In the fourth we may group the purine drugs, caffeine, theobromine, theocine and also the newer preparations containing calcium, salicylates, etc. Digitalis makes up the fifth group.¹⁷

Restrictions in fluids (Karell regimen) or in sodium chloride (salt-poor or salt-free diet) were frequently resorted to, but for periods of many months in succession urea was the only measure used for combating edema, and no restrictions were made with regard to the quantity of water and salt within ordinary dietary limits. Throughout other stretches of many months urea was the sheet anchor of diuretic therapy, but from time to time required supplementation with mersalyl or other diuretics, or more stringent supervision of the intake of water and salt. Without entering into too many details, it may be said that our general plan consisted in ridding the patient of edema and restoring cardiac function as soon and as efficiently as possible, and we learned that this could often be accomplished expeditiously by massive doses of urea often with interval doses of mersalyl. Digitalis was not necessary. The response was equally good in the congestive failure state, whether or not the patient was suffering from auricular fibrillation. The patients who reached the hospital in previous years, i. e., before we began to give urea in massive doses, went through preliminary treatment with all the remedial agents then known, but for them, also, we finally learned to lean chiefly on urea for daily treatment. Whatever the antecedent treatment, urea became the mainstay in the cases here reported; the patients remained edema-free, usually ambulatory, restored in cardiac competency to a noticeable degree and able to take fluids and sodium chloride without hampering regulations.

We have reached the following conclusions in regard to the prolonged administration of urea in massive doses in the treatment for cardiac dropsy: 1. A marked drop in body weight results from the loss of fluids. That this loss is not flesh may be deduced from the fact that the patients in the cases reported received a diet of adequate calories (about 2,000 per day), and that they did not grow asthenic or emaciated and so-called cardiac cachexia did not develop. 2. The loss in

¹⁷ The hormone products go to make up a sixth group, that is, pituitary extracts as used in diabetes insipidus, thyroid substances in nephrosis and parathormone in cardiovascular renal edema. These products were not given in the cases here reported.

edema was greatest and most noticeable when there was pronounced congestive heart failure, subsequently, as the edema became milder its disappearance was not so spectacular. Excluding a few cases that proved to be refractory to urea, the diuretic action of urea was seldom lost completely unless and until the cardiac reserve was at a very low ebb and restoration of cardiac competency, to any appreciable degree, was no longer possible. 3 Urea was seen to stabilize the body weight at a fairly constant level over months, once this level was attained, it never reverted to the original water-logged body weight as long as urea therapy was kept up. This residual edema-free weight became quite stationary, varying but a few pounds, if at all, over months.

In the presence of this residual almost stationary, edema-free weight there were a number of distinguishing features. (a) Signs of congestive heart failure were not present. With apparently good heart function and steady unchanging weight, the question arose, was urea really acting to prevent the reaccumulation of edema, or did the edema fail to reappear because of the improved state in the cardiovascular system? While we cannot speak categorically, we believe that probably both factors played significant rôles, and we have suggestive evidence that urea was by no means secondary or negligible in usefulness (case 2 and the case of W. T.). When the cardiac reserve was very poor, however, the danger of heart failure was imminent, especially if a new complication, such as a respiratory infection, ensued, and this despite the fact that congestive signs were absent and that urea was being taken in sufficient quantities.¹⁸ Therefore, in estimating the complete loss of edema and the congestive signs, one should exclude, by fluoroscopy, signs of partial or incomplete cardiac insufficiency that had failed to spread beyond the confines of the pulmonic and hepatic circuits. These latter changes were seen to linger long after the "external," more discernible signs disappeared, and such patients might, therefore, have been erroneously labeled edema-free and without cardiac insufficiency.

(b) A second distinguishing feature was the fact that mersalyl had little effect at this stage. (Our charts often showed that some eager advisor ordered mersalyl when it was not needed.)

(c) The patients at this stage, i. e., with a residual edema-free weight, enjoyed an improved state of cardiac reserve as far as was compatible with the underlying cardiovascular derangement.

To summarize, urea did not lose its diuretic effect over long periods of time, and it helped maintain the patient's weight at a constant

18 After the "external" signs of edema disappear, the patient may still reveal, on fluoroscopy, lung stasis, engorgement of the secondary pulmonic branches and left auricular enlargement. These fluoroscopic findings speak for the continued presence of cardiac insufficiency, further or increased doses of urea are indicated.

residual, edema-free level¹⁹ Moreover, this equilibrium in body weight served as an excellent guide in watching for disturbances in cardiac competency or in estimating the continued diuretic efficacy of urea

THE INNOCUOUSNESS OF THE PROLONGED USE OF MASSIVE AMOUNTS OF UREA

In estimating the possible injurious effects from the prolonged use of urea, we have three means at hand (1) clinical observations and impressions, (2) laboratory investigations on renal function and (3) histologic study of the kidney structures

1 Observation of cases continuously for many months, as was done under rather unchanging external circumstances in our study, enforced

TABLE 6—*Results of Concentration Tests of the Urine and Studies of the Blood Chemistry in the Five Cases Reported*

Case	History No	Auricular Fibrillation	Before Urea Therapy		Days on Urea	Days in Hospital	After Urea Therapy	
			Urinary Specific Gravity	Blood Urea Nitrogen, Mg			Urinary Specific Gravity	Blood Urea Nitrogen,* Mg
1	58046	+	1 033 1 035	24 2	243	361	1 016 1 026	24 2
2	61686	+	1 008 1 027	17 4 9 6	333	478	1 013 1 026	17 4 26 0
3	60139	0	1 014 1 020	18 6 13 0	606	606	1 017 1 027	18 6
4	60249	0	1 018 1 009	15 0	730	730	1 024 1 034	15 0
5	53316	0	1 012 1 024	18 2 15 1	1 067	1,390	1 012 1 015	24 2 20 2

* These figures were obtained after urea had been withheld for several days before the test was performed

the belief that urea, as we gave it, induced no outward results except for occasional gastro-intestinal distress in the way of nausea or vomiting, or occasionally diarrhea

2 The laboratory tests did not disclose any disturbance in renal function attributable to urea In four patients there was no change whatsoever In one case (case 5), there were no signs of renal impairment on admission or for many months later Subsequently, although urea served well as a diuretic, an underlying, developing arteriolar disease, confirmed at autopsy, manifested itself by a moderate impairment of renal function, i e, the specific gravity of the urine became 1 012 and 1 015 A more detailed survey of the values of the blood urea of this patient disclosed that, with few exceptions, the figures fell promptly when urea was stopped, and that as late as Jan 20, 1930, the blood urea nitrogen was 20 2 mg after a three day withdrawal of the drug

¹⁹ Seasonal variations, and also fever from one cause or another, were not without some influence on the body weight

Concentration tests of the urine and studies of the blood chemistry, carried out after long periods during the use of urea, demonstrated little or no difference from the values obtained soon after the patients were admitted to the hospital. These results are adequately illustrated in table 6 and call for no further comment.

3 The effect of urea was determined by histologic examination of the kidney. We were able to secure microscopic preparations of the kidney from three patients (nos 4904, 14301 and 18357) who took massive doses of urea intermittently during many months. In none did we find a pathologic alteration that could be attributed to the urea. In fact, the histologic appearance was normal except in one other case (case 5), in which a concomitant arteriolar change had taken place. Urea, therefore, in the doses and manner employed by us is without demonstrable effect on the renal structures.

MASSIVE DOSES OF UREA AS A PROPHYLACTIC AGAINST THE REACCUMULATION OF EDEMA

With the greater part of the edema fluid out of the body, urea will still mobilize any lingering or residual edema, the latter often indicating a temporary or mild degree of cardiac insufficiency. There comes a time, however, when the heart rights itself functionally and edema is entirely absent, as nearly as one can tell, and the further use of urea is unnecessary. We could not always recognize the point at which cardiac sufficiency was entirely restored and called for no further diuretic therapy. From a practical standpoint, therefore, we believed it more prudent not to halt the administration of urea, although in some cases it probably no longer played a part in preventing the recurrence of edema.

Under such circumstances, it was natural, as already indicated, to speculate whether edema failed to reappear because the heart was no longer insufficient or because the urea acted as a preventive. Our evidence, though indirect, supports the latter point of view. We observed patients, who, while taking urea, were seemingly restored to good cardiac function over long periods, free from edema and stationary in weight,²⁰ but in whom, when urea was discontinued, clinical signs of insufficiency soon developed and a rise in weight occurred, these signs disappeared when urea was resumed.

Two cases illustrate this change: case 2, already described, and the case of Mrs. W. T., aged 42, a private patient of one of us (Dr

²⁰ A small elevation in weight, of itself, say from 3 to 5 pounds (1.4 to 2.3 Kg.), was not always an infallible mark of the return of cardiac insufficiency, because such variations were governed by a variety of extracardiac circumstances, such as an increase in body flesh, changes in external temperature and humidity or a subsidence of a concomitant fever.

Miller), who had intense heart failure with extensive anasarca three and a half years prior to the writing of this article due to an advanced, chronic, rheumatic, valvular disease associated with permanent auricular fibrillation. She remained edema-free, stabilized in weight, at from 130 to 134 pounds (59 to 60.8 Kg), and restored almost to the activity of a normal person while taking 70 Gm of urea three or four days a week from Feb 28, 1928, until July 20, 1931. During these months, she also received eighty-nine injections of mersalyl, the last one on April 10, 1931, and occasional doses of digitalis to control the heart rate. As a test, on May 9, 1931, with the weight at 131 pounds (59.4 Kg) and as she had felt well and fit for months, the urea was discontinued. Within nine days, unmistakable dyspnea, increased cyanosis, edema of the ankles and tenderness of the liver developed and her weight increased 8 pounds (3.6 Kg) (139 pounds [63 Kg]). She became and felt sick, but was quickly restored with diuretics, taking no digitalis.

Such occurrences permit us to believe that urea is valuable in preventing the return of edema, and in this way provides another safeguard for cardiac patients with a restricted reserve in whom edema might otherwise reappear on a slight provocation.

CONCLUSIONS

1 Urea administered in the way described has been found to be an effective diuretic over long periods of time in selected cases. Whereas it can function alone over many months in keeping the patient edema-free, it may require the supplemental use of other diuretics. This is true for the patient with or without auricular fibrillation. Cases are reported in which its unbroken administration continued over three years.

2 Urea does not impair the function of the kidneys or alter their histologic structure after prolonged administration.

3 Once the signs of congestive heart failure have been removed, urea is valuable in preventing their recurrence. The drug tends to maintain the patient's weight at a low and constant edema-free level over months and even years. During such periods, our patients often required little or no restrictions of the intake of fluid or salt within ordinary dietary limits.

TRYPTOPHANURIA AND ITS SIGNIFICANCE

A PRELIMINARY REPORT

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It came to my attention about two years ago, as previously reported in the ARCHIVES,¹ that the Boltz test for tryptophan may be applied directly to urine, and, as very few data on the incidence of tryptophan in urine are available, it seemed to me that this problem was one worthy of the expenditure of some time and energy. This paper is consequently a report of the results of 169 tests on 10 normal controls, indicating that tryptophan is not eliminated in the urine of the normal man in health and on an average diet, of 525 tests on specimens sent to the laboratory for routine examination from general surgical and medical cases, and of over 600 tests on specimens from cases of nervous and mental diseases—all accumulated during the past eighteen months.

An essential improvement in the technic of the original Boltz test when employed in urinalysis has been found to consist in cooling the tube containing the test solutions during the addition of the sulphuric acid. This keeps down to a minimum the production of interfering yellow and brown colors, and renders the test much simpler to read with certainty, as evidenced by the fact that it has been easily learned by other technicians. As now employed the test is conducted as follows:

EXPERIMENTAL DATA

Technic—Place in a small glass test tube 1 cc of the filtered or centrifugated specimen to be examined.

Add 0.3 cc of acetic anhydride and shake.

While the tube is held under the tap or in a large beaker of cold water, add 0.8 cc of concentrated sulphuric acid from a pipet, a drop at a time, and shake.

Let the tube stand at room temperature under observation for five minutes.

The positive reaction is indicated by the appearance of color varying from light lilac to deep purple. The color is unmistakable by daylight, as normal specimens range from light to dark brown, but the test is practically impossible to read by any of the artificial lights with which I have experimented up to the time of writing.

Experimental Observations—During the course of the application of the test to date, the following observations having a technical bearing have been made. Positive specimens left standing at room temperature over night without a preservative have shown in the morning considerable growth of bacteria and have been found negative by the test. The

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1 Brice, A. T. The Boltz Test in Urinalysis, Arch Int Med 46 778 (Nov) 1930

same specimens preserved with a few drops of chloroform, ether or toluene remained positive. By the addition of a few drops of toluene, specimens kept at room temperature in stoppered flasks have been preserved for as long as a month. Mercuric chloride solutions precipitate tryptophan from urine and preserve it against bacterial decomposition.

Twenty specimens from general surgical and medical cases giving positive Boltz reactions in the presence of acetone and diacetic acid have been observed and recorded. Seven specimens from five different cases of diabetes mellitus have been observed and recorded positive for tryptophan by the Boltz test in the presence of sugar. The presence of acetone, diacetic acid and sugar, even in considerable amounts, therefore, does not necessarily mask a positive Boltz test. The removal of ammonia by permuted, of phosphates and carbonates by barium chloride and hydroxide or of carbohydrates by copper sulphate and calcium hydroxide from the average specimen of urine does not appreciably simplify the reading of the Boltz reaction or increase its sensitiveness through any clarification of interfering colors. The exact sensitiveness of the test up to the present time has not been determined. It is believed to be amply sensitive to demonstrate a clearcut and easily readable reaction with pathologic positives.

Pathologic Observations—Tryptophan was found to be present in 33 per cent of 525 specimens examined from general surgical and medical cases. Of 313 of these specimens that were positive for albumin, 91, or 29 per cent, were also positive for tryptophan. The highest incidence of tryptophan in combination with albumin of any group of specimens from similar cases was shown by the group of 25 specimens from 9 different cases of degenerative diseases of the kidneys, 18 of which, or 72 per cent, were also positive for tryptophan. The finding of 222 specimens positive for albumin by the usual routine tests which were negative for tryptophan by the Boltz test indicates the existence of albuminurias in which the protein molecule eliminated does not contain a tryptophan group. A total of 169 specimens in this series was found positive for tryptophan by the Boltz test, of which number 78 or 46 per cent of the positives were albumin-free. This indicated the existence of a tryptophanuria as a clinical entity distinct from albuminuria.

The highest incidence of free tryptophan not in combination with albumin was found in a small group of 5 cases of nervous disorders, such as neuritis, neurasthenia, hysteria, neuroirititis, and such as occur during menopause, and in 7 cases of surgical shock, such as amputation, gunshot and other wounds, fracture, dislocation and secondary hemorrhage. The figures, while meager, led me none the less to the conclusion that tryptophanuria as a distinct clinical entity might most likely be found in the group of nervous and mental disorders. This conclusion has been partially

verified by the examination during the past three months of over 600 specimens from 101 cases of mental disease, as follows: miscellaneous diagnoses, 7, dementia paralytica, 7, manic-depressive psychosis, 7, and dementia praecox, 80. The average incidence of specimens positive for tryptophan was slightly less than that for those from general surgical and medical cases, being but 21 per cent, this finding, however, representing almost entirely free tryptophan not in combination with albumin. Of the 101 cases examined by the test, 8 in the dementia praecox group have been found in which tryptophanuria was consistently present with no concurrent albuminuria.

The evidence is rather strongly indicative that tryptophanuria in nervous and mental disease is most likely to occur during periods of hyperactivity. This conclusion was arrived at by a consideration of the findings in individual cases and is supported by the following figures: Of 350 specimens taken at random from the 4 halls of a ward of the United States Veterans Hospital at Palo Alto, 50 specimens, or slightly over 14 per cent, were found positive, while of 258 specimens taken in the tub room of the same ward, 79, or about 31 per cent, were positive.

The findings with reference to the effect of tubs and packs indicate that this treatment is more likely to increase tryptophanuria than to diminish it, and that the extent of the increase is proportional to the length of time of such treatments as follows: Of 113 specimens examined just prior to the treatment, 27 per cent were found positive. Of 91 specimens examined after from two to four hours of the treatment, 31 per cent were found positive. Of 29 specimens examined after from five to seven hours of the treatment, 34 per cent were found positive. Of 25 specimens examined after over seven hours of the treatment, 40 per cent were found positive.

The patients and staff of the United States Veterans Hospital No. 24, and in particular those of ward No. 17 gave valuable cooperation and assistance in carrying out this series of tests.

SUMMARY AND CONCLUSIONS

1. An improved technic for the application of the Boltz test to the detection of tryptophan in urine is presented.

2. The application of the test is not interfered with by the presence of sugar, albumin or acetone and diacetic acid in the specimen.

3. The findings to date indicate the existence of albuminurias in which no tryptophan group is associated with the protein molecule eliminated and also of an uncomplicated tryptophanuria.

4. Tryptophanuria as evidenced by a positive Boltz reaction undoubtedly signifies some underlying derangement of protein metabolism, though its exact pathognomonic significance, if any, is as yet not clearly understood.

CALCIUM STUDIES

VII THE CALCIUM AND INORGANIC PHOSPHORUS CONTENT OF CELEBROSPINAL FLUID AND BLOOD SERUM IN CHRONIC GLOMERULONEPHRITIS WITH UREMIA

A CANTAROW, M D

PHILADELPHIA

Since Greenwald¹ in 1915 reported the observation of an increase in the concentration of inorganic phosphorus in the blood serum of patients with nephritis, many investigators have studied the inorganic constituents of the blood and other body fluids in renal disease. Marriott and Howland² appear to have been the first to report the occurrence of hypocalcemia in renal failure a phenomenon they attributed to the increase in the concentration of serum phosphate. They also suggested that the latter factor is of importance in the production of nephritic acidosis. The intimate relationship between hyperphosphatemia and hypocalcemia was soon after demonstrated by Binger,³ who showed that the intravenous injection of phosphates is followed by a diminution in the concentration of serum calcium. Subsequent studies have confirmed these observations and have in part supported the conception of the etiologic relation of hyperphosphatemia to hypocalcemia in nephritis. Halverson, Mohler and Bergeim⁴ found serum calcium values as low as 7 mg per hundred cubic centimeters in some cases of nephritis. Feigl,⁵ in a series of patients with renal disease, found the serum inorganic phosphorus to vary from 7.2 to 14.5 mg and the serum calcium from 7.4 to 10.3 mg per hundred cubic centimeters. Denis and Hobson⁶ observed phosphorus values as high as 10 mg and calcium values as

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1 Greenwald, I. The Estimation of Lipoid and Acid-Soluble Phosphorus in Small Amounts of Serum, *J Biol Chem* **21** 29, 1915

2 Marriott, W. McK., and Howland, J. Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, *Arch Int Med* **18** 708 (Nov.) 1916

3 Binger, C. Toxicity of Phosphates in Relation to Blood Calcium and Tetany, *J Pharmacol & Exper Therap* **10** 105, 1917-1918

4 Halverson, J. O., Mohler, H. K., and Bergeim, O. The Calcium Content of the Serum in Certain Pathological Conditions, *J Biol Chem* **32** 171, 1917

5 Feigl, J. Neue Beiträge zur Kenntnis der anorganischen Stoffe des Blutes. I. Kationen und Hyperphosphatämie bei Morbus brightii, *Ztschr f physiol Chem* **3** 280, 1920

6 Denis, W., and Hobson, S. A Study of the Inorganic Constituents of the Blood Serum in Nephritis, *J Biol Chem* **55** 183, 1923

low as 76 mg. In an earlier report Denis and Minot⁷ noted serum phosphorus concentrations as high as 40 mg per hundred cubic centimeters.

The clinical significance of these observations has been the subject of considerable discussion and speculation. Most observers believe that hyperphosphatemia in nephritis is a direct result of renal functional insufficiency and, as pointed out by Marriott and Howland,² is an important factor in the production of acidosis. However, Denis and Minot⁷ found that the degree of phosphatemia bore no definite relation to the state of the alkaline reserve or to the degree of nonprotein nitrogen retention in the blood. In spite of this they made the observation that the serum phosphate level is of definite prognostic significance as in the nonfatal cases in their series, although the patients were seriously ill, they exhibited little or no phosphate retention. Schmitz, Rhodenburg and Myers⁸ stated that a low plasma carbon dioxide combining power may be present in association with a normal serum phosphate concentration in nephritis, but that a high serum phosphate concentration is almost invariably accompanied by a low plasma carbon dioxide capacity. They also emphasized the prognostic significance of hyperphosphatemia in renal disease, but believed it to be of less value than creatinine retention. De Wesselow⁹ found that the concentrations of urea and inorganic phosphorus in the blood paralleled each other, and he believed that uremic symptoms are related more directly to the latter than to the former.

In attempting to determine the significance of hypocalcemia in nephritis, one encounters a much more complex problem. Following the suggestion of Marriott and Howland² and the experimental work of Bingei,³ the earlier investigators attributed the diminution in serum calcium entirely to the increased serum phosphate concentration. In 1923, however, Salvesen and Linder¹⁰ demonstrated the existence of a parallelism between the serum protein and serum calcium concentrations, showing that in cases of renal disease with diminution in the level of serum protein there is a corresponding decrease in the serum calcium concentration which is independent of any alteration in the serum phos-

7 Denis, W., and Minot, A. S. A Study of Phosphate Retention from the Standpoint of Blood Analysis, *Arch Int Med* **26** 99 (July) 1920.

8 Schmitz, H. W., Rhodenburg, E. L., and Myers, V. C. The Inorganic Phosphorus and Calcium of the Blood in Nephritis, *Arch Int Med* **37** 233 (Feb.) 1926.

9 de Wesselow, O. L. V. On the Phosphorus and Calcium of the Blood in Renal Disease, *Quart J Med* **16** 341, 1923, The Immediate Prognosis in Nephritis. With Some Remarks on Uremia, *Lancet* **2** 163, 1923.

10 Salvesen, H. A., and Linder, G. C. Observations on the Inorganic Bases and Phosphates in Relation to the Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure. *J Biol Chem* **58** 616 1923.

phate level Rona and Takahashi¹¹ several years before, and many observers since that time, had established the partition of serum calcium into diffusible and nondiffusible fractions, the latter being in all probability in combination with serum protein. This observation was borne out by the work of Salvesen and Linder¹⁰. Not only did they find a parallelism between changes in serum protein and calcium, but they also noted that the calcium content of practically protein-free edema fluids in renal and cardiac disease corresponded closely to the diffusible fraction of the serum calcium. However, the values (from 50 to 70 per cent) given by them as normal for this fraction are higher than those accepted at the present time. The observation was made that in two patients with uremia the decrease in calcium was out of proportion to the fall in protein and that in such cases the degree of hypocalcemia was proportional to the increase in serum phosphate. Since then Loeb and Nichols¹² and Hastings, Murray and Sendroy¹³ have shown that the solubility of calcium in both true and artificial serum is increased by proteins, probably through the formation of an un-ionized, nondiffusible calcium-protein complex. It would therefore be expected that any diminution in serum protein, other things being equal, should be associated with a decrease in the concentration of serum calcium, the diminution occurring entirely in the nondiffusible fraction. Such findings have been reported in nephritis and nephrosis by Liu,¹⁴ Scriver,¹⁵ Cantarow,¹⁶ Peters and Eiserson¹⁷ and Bennett, Dodds and Robertson¹⁸.

11 Rona, P, and Takahashi, D. Beitrag zur Frage nach dem Verhalten des Calciums in Serum, *Biochem Ztschr* **49** 370, 1913.

12 Loeb, R. F. On the Diffusibility of the Calcium of Blood Serum Through Collodion Membranes. The Effect of Sodium Chloride and Changes in Hydrogen-Ion Concentration, *J. Gen. Physiol.* **6** 453, 1924, The Effect of Pure Protein Solutions and of Blood Serum on the Diffusibility of Calcium, *ibid.* **8** 451, 1926. Loeb, R. F., and Nichols, E. G. Factors Influencing Diffusibility of Calcium in Human Blood Serum, *J. Biol. Chem.* **72** 687, 1927, Effects of Dialysis and of Ether Extraction on Diffusibility of Calcium in Human Blood Serum, *ibid.* **74** 645, 1927.

13 Hastings, A. B., Murray, C. D., and Sendroy, J., Jr. Studies of Solubility of Calcium Carbonate in Salt Solutions and Biological Fluids, *J. Biol. Chem.* **71** 723, 1926-1927.

14 Liu, S. H. The Partition of Serum Calcium into Diffusible and Nondiffusible Portions, *Proc. Soc. Exper. Biol. & Med.* **24** 817, 1927, *Chinese J. Physiol.* **1** 331, 1927.

15 Scriver, W. deM. Observations on the Excretion of Calcium in Two Cases of Nephrosis Treated with Parathyroid Extract, *J. Clin. Investigation* **6** 115, 1928.

16 Cantarow, A. Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1931, p. 97.

17 Peters, J. P., and Eiserson, L. The Influence of Protein and Inorganic Phosphorus on Serum Calcium, *J. Biol. Chem.* **84** 155, 1929.

18 Bennett, T. I., Dodds, E. C., and Robertson, J. D. The Conception of "Nephrosis" Observations on Three Fatal Cases, *Quart. J. Med.* **24** 239, 1931.

Several authors have attempted to show some relationship between the serum calcium level and uremic manifestations. Bennett¹⁹ reported a case with serum calcium values ranging between 5.9 and 6.6 mg and inorganic phosphorus from 6.2 to 8.5 mg per hundred cubic centimeters, the carbon dioxide combining power of the blood plasma varying from 56 to 12.6 per cent by volume. The low calcium concentration persisted throughout the variations in the degree of acidosis, and the author expressed his belief in the possible existence of a relationship between the neuromuscular phenomena of uremia and those of tetany. Similarly, de Wesselow⁹ stated that the hypocalcemia of nephritis with uremia, associated with phosphate retention, may be the underlying cause of the generalized tremors and localized twitchings commonly observed in such patients. Schmitz, Rohdenburg and Myers⁸ found that nine of thirteen patients with renal disease with serum calcium values below 7 mg exhibited convulsions or muscular twitchings, and they concluded that a relatively high proportion of cases of terminal glomerulonephritis presenting these manifestations are found to have subnormal serum calcium concentrations.

It is unfortunate that until comparatively recently no attempt was made to identify accurately the true nature of the renal lesion and metabolic disturbance in patients with renal disease associated with hypocalcemia. In nephrosis and in nephritis with a superimposed nephrotic lesion, hypocalcemia, when present, is due largely to the diminution in serum protein which commonly occurs in association with degenerative kidney lesions. In advanced chronic glomerulonephritis with renal failure, on the other hand, hypocalcemia, when present, is primarily a result of an increase in the concentration of serum phosphate. The relationship between the concentrations of protein, calcium and phosphorus in serum has been defined by Peters and Eiserson¹⁷ by the equation $Ca = 7 + 0.556 \text{ protein} - 0.255 P$, which is applicable in conditions not associated with any primary disturbance of calcium phosphate metabolism. Advances in knowledge of the factors involved in the maintenance of the normal calcium and phosphorus concentrations in the blood have greatly clarified the understanding of the changes in those elements which occur in renal disease. Very few data are available, however, as regards the distribution of calcium and phosphorus between the blood and cerebrospinal fluid in various types of renal disease. Such data should afford some insight into the distribution of calcium and phosphorus in the tissue fluids and, consequently, might shed some light on the significance of hypocalcemia in nephritis and on its relation to the development of certain clinical manifestations of uremia.

19 Bennett, T. I. Some Problems of Nephritis, *Lancet* 1 535, 1928

The present study consists of an analysis of fourteen cases of advanced glomerulonephritis with uremia. The reported data consist of the following determinations: blood creatinine, total serum protein, serum albumin and globulin, serum calcium, serum phosphate, plasma carbon dioxide combining power and cerebrospinal fluid calcium and phosphate. The protein content of the cerebrospinal fluid was not determined quantitatively, but in no case was an increase evidenced by the Noguchi qualitative method. All blood and cerebrospinal fluid

*Relationship Between Concentrations of Calcium and Phosphorus in Blood
Serum and Cerebrospinal Fluid in Fourteen Patients with Advanced
Nephritis With and Without Hypoproteinemia*

Cases	Blood							Spinal fluid		Ratio Spinal Fluid Cal eum, per Cent	Ratio Spinal Fluid Phos phorus, per Cent
	Serum Creat inine, Mg per 100 Ce	Serum Pro tein, Gm per 100 Ce	Serum Albu min, Gm per 100 Ce	Carbon				Phos phorus, Mg per 100 Ce	Cal cium, Mg per 100 Ce		
				Serum Glob ulin, Gm per 100 Ce	Carbon Dioxide Capac ity, per Cent by Volume	Serum Phos phorus, Mg per 100 Ce	Serum Cal cium, Mg per 100 Ce				
1 T C	23.4	7.21	4.62	2.62	29	18.7	7.02	7.2	3.47	19.1	.85
2 S G	11.5	6.45	4.13	2.32	22	10.5	8.51	4.0	1.08	47.9	.88
3 H I	15.0	6.82	3.94	2.88	31	8.6	8.12	3.3	4.32	51.3	.383
4 J R	10.5	6.21	3.81	2.40	28	8.8	8.56	2.1	3.83	41.7	.386
5 J T	17.4	7.02	1.12	2.90	19	12.1	8.10	4.7	3.65	45.0	.88
6 M V	18.0	6.35	3.31	3.04	24	9.4	9.02	3.5	4.12	45.6	.372
7 R F	13.7	6.78	3.62	3.16	16	14.2	7.93	5.7	3.26	41.1	.101
8 S A	10.2	7.16	4.08	3.08	20	10.8	8.51	1.2	3.75	43.9	.388
Average							8.26	4.5	3.81	46.1	.386
9 T M	15.8	1.22	2.06	2.16	26	7.3	7.40	3.1	4.13	55.8	.124
10 A F	9.6	3.18	1.15	1.73	23	9.8	7.13	3.5	3.82	53.5	.757
11 T S	11.0	3.66	1.60	2.06	18	11.6	7.22	4.5	4.04	55.9	.396
12 L M	12.5	1.31	2.15	2.19	19	8.4	7.61	3.1	3.96	52.0	.104
13 W G	11.5	3.05	1.38	1.67	21	8.4	6.81	3.1	4.31	63.0	.369
14 J W	3.4	3.67	1.61	2.03	47	3.5	8.25	1.1	5.05	61.0	.311
Average							7.41	3.1	4.21	56.8	.376
Total average		5.14				10.1	7.89	3.9	3.93	50.7	.352

studies in each case were made on specimens withdrawn simultaneously. Total serum proteins were determined by a micro-Kjeldahl method employing direct nesslerization,²⁰ serum albumin by the method of Howe²¹ and serum globulin by subtracting albumin from serum protein. Calcium determinations were made by the Clark-Collip modification of

²⁰ Hawk, P. B., and Bergeim, O. Practical Physiological Chemistry, ed 10, Philadelphia, P. Blakiston's Son & Company, 1931, p. 449.

²¹ Howe, P. E. The Determination of Proteins in Blood. A Micro Method, J Biol Chem 49 109, 1921.

the Kramel-Tisdall procedure,²² and inorganic phosphorus by the method of Fiske and Subbarow.²³ Creatinine was determined by the method of Folin,²⁴ and the plasma carbon dioxide capacity by the manometric method of Van Slyke.²⁵

All of the patients in this series exhibited high grades of nitrogen retention, the blood creatinine values ranging from 3.4 to 23.4 mg per hundred cubic centimeters, all but one (case 14, J W) being above 9.6 mg. All presented features characteristic of chronic glomerulonephritis, six (cases 9 to 14) showing evidence of superimposed nephrotic lesions. Muscular hyperirritability was present in cases 1, 5, 7, 8, 10 and 12, manifested by generalized tremors, localized muscular twitchings or generalized or localized convulsions.

SERUM PROTEINS

The total serum protein concentration ranged from 3.05 to 7.24 Gm per hundred cubic centimeters, serum albumin from 1.38 to 4.62 Gm and serum globulin from 1.67 to 3.16 Gm. Edema of varying degree was present in cases 9 to 14, the total serum protein content in this group ranging from 3.05 to 4.34 Gm, the serum albumin from 1.38 to 2.15 Gm and the serum globulin from 1.67 to 2.19 Gm. These findings are in accord with the observations of most recent investigators, which indicate that edema is usually present with serum albumin values below 2 Gm per hundred cubic centimeters if the total protein concentration is below 5 Gm (Lester²⁶). The serum protein content bore no discernible relation to the degree of renal insufficiency.

SERUM AND CEREBROSPINAL FLUID PHOSPHATE

The inorganic phosphorus concentration of the serum varied from 3.5 to 18.7 mg per hundred cubic centimeters, being above 7 mg in all but one case (case 14). The degree of hyperphosphatemia roughly paralleled the degree of creatinine retention and of acidosis as indicated by the diminution in the carbon dioxide combining power of the blood plasma. The latter relationship, however, was not invariable, for cases

22 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461, 1925.

23 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J Biol Chem* **66** 375, 1925.

24 Folin, O. Laboratory Manual of Biologic Chemistry, ed 4, New York, D Appleton & Company, 1927, pp 165 and 243.

25 Van Slyke, D. D. Portable Form of Manometric Gas Apparatus and Certain Points in Technique of its Use, *J Biol Chem* **73** 121, 1927.

26 Lester, L. Nephrosis, *Medicine* **10** 182, 1931.

3, 4, 12 and 13, with serum phosphate concentrations of 86, 88, 84 and 84 mg, respectively, had carbon dioxide capacity values ranging from 16 to 31 per cent by volume. Furthermore, in case 12, with a carbon dioxide capacity of 19 per cent by volume, the serum phosphate was 84 mg per hundred cubic centimeters, whereas in case 1, with a serum phosphate concentration of 187 mg, the highest observed in this series, the plasma carbon dioxide capacity was 29 per cent by volume. Obviously, factors other than phosphate retention are of importance in the production of a diminished alkali reserve in nephritis. Chief among these appear to be (a) impairment of the ammonia-forming function of the kidneys, as demonstrated by Palmer and Henderson²⁷ and by Van Slyke and his co-workers,²⁸ and (b) depletion of the available base supply of the body by excessive elimination of base in the urine, as shown by Linder²⁹ and Salvesen.³⁰

The inorganic phosphorus of the cerebrospinal fluid varied from 1.1 to 7.2 mg per hundred cubic centimeters, the ratio of cerebrospinal fluid to serum phosphorus ranging from 31.1 to 42.4 per cent (average 38.2 per cent). These figures are in agreement with those of Merritt and Bauer,³¹ who found this ratio to range from 31 to 45 per cent (average 38 per cent) in a group of patients with nonsuppurative disease of the central nervous system. They are somewhat lower than those reported by Hamilton,³² which averaged 50 per cent. If one accepts the premise that the cerebrospinal fluid is a dialysate of the blood plasma, it follows that the serum phosphorus is diffusible to the extent of about 30 to 45 per cent. These observations emphasize the difficulty of interpreting results obtained by in vitro diffusibility studies, and the fallacy of accepting results obtained by such methods as indicative of conditions of diffusibility existing in the living body. For example, Pincus, Peter-

27 Palmer, W. W., and Henderson, L. J. A Study of Several Factors of Acid Excretion in Nephritis, *Arch. Int. Med.* **16**: 109 (July) 1915.

28 Van Slyke, D. D., Linder, G. C., Hiller, A., Leiter, L., and McIntosh, J. F. The Excretion of Ammonia and Titrable Acid in Nephritis, *J. Clin. Investigation* **2**: 255, 1926.

29 Linder, G. C. The Effect of Mineral Acid on Acid-Base Regulation in Health and in Nephritis, *Quart. J. Med.* **20**: 285, 1927.

30 Salvesen, H. A. Variations in the Serum Electrolytes in Diseases of Renal Origin with Special Reference to the Cause of Renal Acidosis, *Acta med. Scandinav.* **69**: 126, 1928.

31 Merritt, H. H., and Bauer, W. The Equilibrium Between Cerebrospinal Fluid and Blood Plasma. III. The Distribution of Calcium and Phosphorus Between Cerebrospinal Fluid and Blood Serum, *J. Biol. Chem.* **90**: 215, 1931.

32 Hamilton, B. A Comparison of the Concentrations of Inorganic Substances in Serum and Spinal Fluid, *J. Biol. Chem.* **65**: 101, 1925.

son and Kramer,³³ employing ultrafiltration through artificial membranes, found that the inorganic phosphorus content of the serum and ultrafiltrate were practically identical, indicating that serum phosphate is completely diffusible. This marked discrepancy can be interpreted only as indicating the distinct difference that exists between *in vivo* and *in vitro* diffusibility. This observation, pointed out by me in previous communications³⁴ dealing with calcium diffusibility, has not been sufficiently emphasized in the literature.

The data reported here, as well as those of Merritt and Bauer³¹ and Hamilton,³² suggest that the *in vivo* diffusibility of phosphorus is influenced by the serum protein content, as is that of calcium. This hypothesis is further supported by the findings of Merritt and Bauer³¹ in meningitis, in which condition an increase in the cerebrospinal fluid protein concentration was associated with an increase in the ratio of cerebrospinal fluid to serum phosphorus from the normal average of 38 per cent to an average of 49 per cent. Grollman³⁵ found that whereas normally all of the serum phosphate was filtrable, in conditions of hypercalcemia, as induced by the injection of parathormone, only 63 per cent was filtrable. In a case of hypoparathyroidism referred to by Albright, Bauer, Cockrill and Ellsworth,³⁶ as the difference between the serum calcium and cerebrospinal fluid calcium diminished, the difference between the corresponding levels of phosphorus increased, and vice versa, suggesting, as stated by the authors, that in hypoparathyroidism the inactivated (nondiffusible) calcium decreases and the inactivated (nondiffusible) phosphorus increases. No such relationship is evidenced in the present series, there being no apparent reciprocal correlation between the ratios of calcium and phosphorus in cerebrospinal fluid and blood serum. The problem in nephritis, however, is complicated by the variation in serum protein which does not play an important part in the disturbance of calcium-phosphate equilibrium in parathyroid dysfunction. The constancy of the cerebrospinal fluid-blood serum phos-

33 Pincus, J. B., Peterson, H. A., and Kramer, B. A Study by Means of Ultrafiltration of the Condition of Several Inorganic Constituents of Blood Serum in Disease, *J. Biol. Chem.* **68** 601, 1926.

34 Cantarow, A. Calcium Studies. V. The Relationship Between the Calcium Content of Cerebrospinal Fluid and Blood Serum, *Arch. Int. Med.* **44** 670 (Nov.) 1929, The Diffusibility of Calcium in Bronchial Asthma and Allied Disorders and in Pulmonary Tuberculosis, *Am. J. M. Sc.* **179** 497, 1930.

35 Grollman, A. J. The Condition of the Inorganic Phosphorus of the Blood with Special Reference to the Calcium Concentration, *J. Biol. Chem.* **72** 565, 1927.

36 Albright, F., Bauer, W., Cockrill, J. R., and Ellsworth, R. Studies on the Physiology of the Parathyroid Glands. II. The Relation of the Serum Calcium to the Serum Phosphorus at Different Levels of Parathyroid Activity, *J. Clin. Investigation* **9** 659, 1931.

phorus ratio in this group of patients may be only apparent, the influence of the varying serum protein concentration being masked by simultaneous variations in the calcium content of serum and cerebrospinal fluid

SERUM AND CEREBROSPINAL FLUID CALCIUM

The serum calcium concentration in the entire group varied from 6.84 to 9.02 mg per hundred cubic centimeters, the average being 7.89 mg. In the eight patients with normal total protein values, the serum calcium ranged from 7.02 to 9.02 mg, averaging 8.26 mg, in the six patients with hypoproteinemia the serum calcium ranged from 6.84 to 8.25 mg, the average being 7.41 mg. These subnormal values are in agreement with those previously reported and referred to. They illustrate graphically the influence of the serum proteins and phosphate on the serum calcium concentration. In the group of eight patients with normal serum protein values (cases 1 to 8), the calcium values are slightly higher than in the other six patients owing to the fact that in the former hyperphosphatemia alone is exerting a hypocalcemic influence, whereas in the latter the existence of a superimposed state of hypoproteinemia exaggerates the effect of the increased phosphate concentration. It is interesting to note the close agreement of the observed average serum calcium concentration with the calcium value calculated from the protein and phosphorus concentrations on the basis of the formula suggested by Peters and Eiseison¹⁷ $3.02464 (0.556 \text{ protein}) - 2.01195 (0.225 \text{ P}) + 7 = 8.01 \text{ (Ca)}$. The calculated value, 8.01 mg, is only 1.5 per cent (0.12 mg) higher than the observed value, 7.89 mg, substantiating the fundamental integrity of the quantitative expression of the equilibrium between serum protein, phosphate and calcium as elaborated by Peters and Eiseison¹⁷.

The cerebrospinal fluid calcium concentration in the entire series ranged from 3.26 to 5.05 mg per hundred cubic centimeters, averaging 3.98 mg. Eliminating from consideration case 14, in which the serum and spinal fluid phosphate concentrations were within nominal limits, the highest spinal fluid calcium value was 4.31 mg. In cases 1 to 8, with hyperphosphatemia but with normal serum protein values, the spinal fluid calcium values ranged from 3.26 to 4.32 mg, averaging 3.81 mg, in cases 9 to 13, with both hyperphosphatemia and hypoproteinemia, the spinal fluid calcium varied from 3.82 to 4.31 mg, averaging 4.05 mg, in case 14, with normal serum phosphate and low serum protein values, the spinal fluid calcium was 5.05 mg. The normal range, as obtained in a large series of cases previously reported,³⁷ is from

37 Cantarow, A. *Calcium Studies. IV. The Calcium Content of Cerebrospinal Fluid*, Arch. Int. Med. **44**: 667 (Nov.) 1929.

4.5 to 5.5 mg, constituting from 45 to 55 per cent of the total serum calcium concentration. It appears that in nephritis with hyperphosphatemia the cerebrospinal fluid calcium concentration is subnormal. That this decrease is dependent on an increase in serum phosphate rather than on a diminution in serum protein is evidenced by the normal level observed in case 14 and by the observation that the average spinal fluid calcium concentration in cases 9 to 13 was higher than in cases 1 to 8, despite the fact that in the former group the serum calcium and serum protein values were distinctly lower than in the latter. It seems, therefore, that the concentration of nondiffusible calcium (protein-bound) has little or no influence on the diffusibility of calcium in nephritis, the cerebrospinal fluid calcium level being independent of changes in the total serum calcium level caused by variations in the serum protein concentration. This is in accord with the generally accepted conception of the partition of serum calcium into diffusible and nondiffusible components.

The ratio of cerebrospinal fluid to serum calcium ranged from 41.1 to 51.3 per cent, averaging 46.1 per cent, in the group with normal serum protein values (cases 1 to 8), and from 52.0 to 63.0 per cent, averaging 56.8 per cent, in the patients with low serum protein values (cases 9 to 14). These figures further emphasize the dependency of the cerebrospinal fluid calcium concentration on serum phosphate variations and its independence of variations in serum protein.

On analyzing the spinal fluid calcium and phosphate values, it appears that there is a roughly reciprocal relationship between these two factors, the calcium concentration diminishing as the phosphate concentration increases. This observation is of great interest in view of the similar relationship that exists between these two elements in the blood serum. It would seem that in nephritis the cerebrospinal fluid inorganic phosphorus content is the factor that determines the concentration of calcium in that fluid in the absence of an increase in its protein content.

CEREBROSPINAL FLUID CALCIUM AND MUSCULAR IRRITABILITY IN UREMIA

The relationship between the serum calcium level and manifestations of muscular hyperirritability in uremia has attracted considerable attention,³⁸ as was indicated previously. Several observers have suggested that the muscular twitchings and generalized tremors that commonly occur in uremia may be dependent on a state of hypocalcemia. This relationship, however, has not been found to be constant, one reason

38 Schmitz, Rohdenburg and Myers (footnote 8) de Wesselow (footnote 9) Bennett (footnote 19)

perhaps being the almost universal failure, until recently, to distinguish hypocalcemia dependent on hypoproteinemia from that dependent on hyperphosphatemia. Very few data are available regarding the diffusibility of calcium in uremia. Pincus, Peterson and Kramer,³⁸ on the basis of ultrafiltration experiments, stated that the decrease in serum calcium in nephritis occurs only in the nondiffusible fraction. However, their data include one case of uremia, with convulsions, in which, with a serum phosphorus value of 15.6 mg per hundred cubic centimeters, the serum calcium was 6.3 mg, of which only 2.8 mg was ultrafilterable, an observation that contradicts the foregoing statement. In view of the fact that only the diffusible fraction of serum calcium is believed to be concerned with the maintenance of normal muscular irritability, the relation of the cerebrospinal fluid calcium concentration to disturbances of this function may be of significance.

In the present series, generalized or localized convulsive seizures, generalized tremors or localized muscular twitchings occurred in cases 1, 5, 7, 8, 10 and 12, with spinal fluid calcium values of 3.47, 3.65, 3.26, 3.75, 3.82 and 3.96 mg, respectively. It is interesting to note that in none of these cases was the total serum calcium concentration below 7 mg, and that in two instances it was above 8 mg. In only one case (case 4) with a spinal fluid calcium content below 4 mg (3.83 mg) were these manifestations of hyperirritability absent. This apparent relationship may be purely accidental. It, however, rests on a much more logical basis than does the relationship between such manifestations and the serum calcium level.

If the muscular hyperirritability of uremia is dependent on a diminution in the concentration of calcium in the spinal fluid or tissue fluids, the mechanism of its production must differ fundamentally from that operative in parathyroid tetany. It is true that in the latter condition studies of the *in vitro* diffusibility of calcium reveal a diminution in the ultrafilterable or dialyzable fraction. However, studies of the *in vivo* diffusibility of calcium, as evidenced by the cerebrospinal fluid calcium concentration, yield quite different results. For example, Cameron and Moorhouse³⁹ found that in acute tetany both serum and spinal fluid calcium tend to approach the same low level, indicating, apparently, that the decrease in diffusible calcium is relatively slight, whereas the nondiffusible calcium may entirely disappear. Similar findings have

39 Cameron, A. T., and Moorhouse, V. H. K. The Tetany of Parathyroid Deficiency and the Calcium of the Blood and Cerebrospinal Fluid, *J. Biol. Chem.* 63: 687, 1925.

been reported by Merritt and Bauer⁴⁰ in human beings and by Morgulis and Perley in dogs⁴¹. These observations emphasize the necessity for distinguishing sharply between diffusibility through living membranes, in contradistinction to artificial membranes.

Further evidence of the fundamental difference between uremic and tetanic phenomena is furnished by the work of Binger,³ who showed that when basic or neutral phosphates are injected intravenously in amounts sufficient to lower the serum calcium, tetany results, but not if acid phosphates are employed. Since the hyperphosphatemia of advanced renal functional insufficiency is invariably associated with acidosis and with an increase in the proportion of acid phosphate in the blood and tissue fluids, the condition is analogous to that existing in the acid phosphate injection experiment of Binger.³ Furthermore, the muscular hyperirritability of tetany is associated with a lowered threshold of excitability by electrical stimulation, a phenomenon that has not often been observed in uremia. In this fact may reside the essential difference between the two hyperirritable states.

SUMMARY

1 Hypocalcemia in advanced nephritis is dependent on hyperphosphatemia, hypoproteinemia or both.

2 The degree of hyperphosphatemia roughly parallels the degree of creatinine retention and acidosis, the latter less consistently than the former. The ratio of cerebrospinal fluid to serum phosphate ranged from 31.1 to 42.4 per cent, averaging 38.2 per cent. These figures fall within normal limits.

3 The *in vivo* diffusibility of phosphorus appears to be influenced by serum protein as is that of calcium, whereas its diffusibility through artificial membranes is apparently not so influenced.

4 There is no apparent reciprocal relationship between the ratios of calcium and phosphorus in cerebrospinal fluid and blood serum as exists in parathyroid dysfunction. The problem is complicated, however, by the variation in serum protein, which does not play an essential part in the disturbance of calcium-phosphate equilibrium in parathyroid dysfunction. The constancy of the cerebrospinal fluid-blood serum phosphorus ratio in nephritis may be only apparent, the influence of the varying serum protein concentration being masked by that of

40 Merritt, H. H., and Bauer, W. The Equilibrium Between Cerebrospinal Fluid and Blood Plasma. IV. The Calcium Content of Serum, Cerebrospinal Fluid and Aqueous Humor at Different Levels of Parathyroid Activity, *J Biol Chem* **90** 233, 1931.

41 Morgulis, S., and Perley, A. M. Studies on Cerebrospinal Fluid and Serum Calcium, with Special Reference to Parathyroid Hormone, *J Biol Chem* **88** 169, 1930.

simultaneous variations in the calcium content of spinal fluid and blood serum

5 The serum calcium concentration ranged from 6.84 to 9.02 mg per hundred cubic centimeters, being lowest in the group of patients with coincident hypoproteinemia and hyperphosphatemia. The observed serum calcium values are in close agreement with values calculated from the protein and phosphorus concentrations on the basis of the formula suggested by Peters and Eiseison.

6 The cerebrospinal fluid concentration ranged from 3.26 to 5.05 mg per hundred cubic centimeters, averaging 3.98 mg. In thirteen cases of hyperphosphatemia the highest spinal fluid calcium value was 4.31 mg. The decrease in this factor is dependent on an increase in serum phosphate rather than on a decrease in serum protein.

7 There is a roughly reciprocal relationship between the concentrations of calcium and phosphorus in the spinal fluid, as in the blood serum, the calcium content diminishing as the phosphate content increases.

8 There appears to be some relationship between the cerebrospinal fluid calcium concentration and manifestations of muscular hyperirritability in uremia, such manifestations occurring with spinal fluid calcium values below 4 mg per hundred cubic centimeters. The mechanism of production of these phenomena in uremia differs fundamentally from that operative in parathyroid tetany.

9 These observations emphasize the distinction that must be made between diffusibility of calcium and phosphorus through living membranes, in contradistinction to artificial membranes.

CARDIAC OUTPUT FOLLOWING ARTIFICIAL PNEUMOTHORAX IN MAN

DICKINSON W RICHARDS, JR, M D

CONSTANCE B RILEY, B A

AND

MABELLE HISCOCK, B A

NEW YORK

Measurements of the cardiac output and of certain other circulatory and respiratory functions have been made in three cases¹ of pulmonary tuberculosis both before and during the establishment of artificial pneumothorax. All three patients were young men and had moderately advanced lesions of one lung, the right in patients F S and A G, the left in patient D R. Summaries of the histories and clinical findings are given at the end of the article.

Relatively large insufflations of air were given each time, the attempt being made to collapse the lung rapidly, in order to demonstrate as clearly as possible the effects of this procedure on the circulation. Nine hundred, 800 and 800 cc were injected into patient D R, with a four day interval between the first and second injections and three days between the second and third. Patient F S received 700, 500, 600 and 600 cc, the intervals between injections being two, two and three days. The third patient, A G, received about 500 cc twice a week, a total of 4,750 cc being given in four and a half weeks.

The various measurements that were made and the data obtained are listed in the accompanying table, and the more important changes occurring during the course of the pneumothorax production in case 3 are summarized in the accompanying chart.

TECHNIC

It is to be noted that the cases were not treated just alike. The respiratory and circulatory studies on D R were made not under basal conditions, but with the patient at rest in bed, three or four hours after the last meal. The technic

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From the Department of Medicine of the College of Physicians and Surgeons and the Presbyterian Hospital

1 These patients were in the tuberculosis service of Dr James A Miller at Bellevue Hospital, and were transferred temporarily to the Presbyterian Hospital where the studies here reported were made. The assistance and cooperation of Dr Miller and members of his staff were received throughout the course of the work.

Respiratory and Circulatory Measurements Before and After Artificial Pneumothorax

Patient and Date	Hour	Pneumo thorax, Cc	Intra thoracic pressure, Cm H ₂ O	Vital Capacity, Liters	Residual Air, Liters	Respirations per Min	Pulse	Expired Air, Liters per Min	CO ₂ Output per Min, Cc	O ₂ Consumption per Min, Cc	Alveolar CO ₂ , Mm Hg	Arterial CO ₂ Content, per Cent by Volume	Arterial Tension, Mm Hg	Oxygenated Mixed Venous CO ₂ , Mm	A-V CO ₂ Difference, per Cent by Volume*	Cardiac Output, Liters per Min†	Oxygen Capacity, per Cent by Volume
D R † Mar 26 30 Apr 1	11 00					15	90	7 08	270	314	40 1			18 3	3 6	7 5	19 9
	3 30					15	86	7 28	267	301	40 8			50 0	4 1	6 1	
	12 10	900	0, -1														
	4 00			2 50 2 00		15	112	7 56	280	332	38 8			51 2	6 0	1 7	
F S Jan 10 17 20 21	8 30			3 40	1 50	22	95	7 17	216	245	40 7	53 0	11 1	49 8	3 6 (3 8)	6 0 (5 7)	17 7
	9 50				1 33		88	5 94	147	208	10 9	57 1		50 2	3 6	4 1	18 6
	11 00	700	-1, -2	1 65	0 85	26	102	6 03	180	227	43 2	55 5	13 5	53 9	3 9 (3 8)	1 6 (4 7)	18 4
	8 30	1,200	-5, -8	2 20		20	102	6 15	153	201	38 1	50 2	40 0	52 5	5 7 (4 8)	2 7 (3 2)	18 4
A G § Feb 20 25 28 5	10 40		0, -1	2 00	0 77	26	105	7 19	169	223	37 6	47 5	36 9	49 0	4 4 (5 1)	3 8 (3 3)	18 2
	10 30																87
	7 25			4 10	0 95	15	79	5 83	181	217	41 2			50 8	3 9	4 6	17 2
	8 15			4 10	1 10	18	88	6 32	193	227	41 5			51 0	3 9	4 9	17 2
6 to 13 14 16, 18 21 23, 26 30 2, 4 7	8 05	500	-6, -7	4 10	1 00	17	88	6 46	191	2 3	42 1	53 8	11 6	51 7	3 9 (4 2)	5 0 (4 6)	94
	8 05	1,500	-2, -4	2 90	0 75	24	100	6 84	187	237	42 5			52 4	4 0	4 7	
	7 57	850	-1, -2	3 65		20	96	6 17	181	233	40 2			50 8	4 4	4 1	
	8 09			3 40		20	93	6 71	180	229	38 5			48 4	4 2	4 3	17 1
23, 26 30 2, 4 7	7 58	900	+1, 0			23	105	6 66	185	234	38 8			49 3	4 4	4 2	97
	7 50			3 15		22	100	6 62	186	233	36 4	49 8	37 0	47 6	4 9 (4 6)	3 8 (4 0)	17 7
		1,000	+1, -2		0 58	24	109	7 04	189	251	37 4	48 2	34 1	48 0	4 7 (6 4)	4 0 (3 0)	17 9
	7 48																92

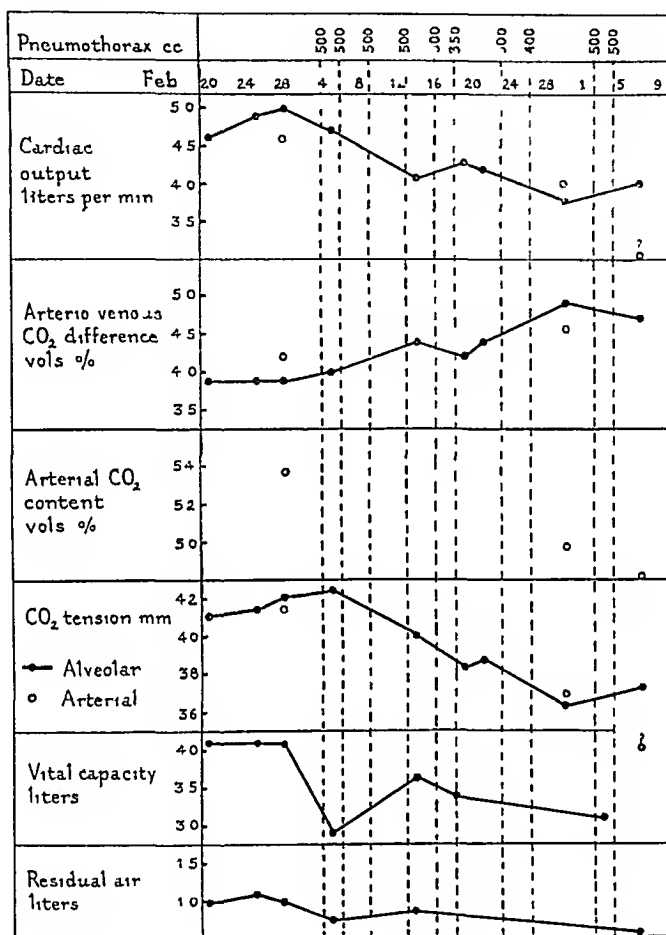
* A-V CO₂ difference is the difference between the carbon dioxide content of arterial and of mixed venous blood

† The figures in parentheses represent cardiac output calculated by the use of arterial blood carbon dioxide content, the other figures, cardiac output calculated by the use of alveolar carbon dioxide tensions

‡ Serum electrolyte measurements (venous blood, under basal conditions) were made on the blood of D R as follows: March 25, 9 10 a m chloride, 102 mM; carbon dioxide, 26 8 mM; phosphorus, 2 mM; protein, 17 8 mM, total base, 149 mM, April 2, 9 00 a m chloride, 103 2 mM, carbon dioxide, 28 1 mM, phosphorus, 2 4 mM, protein, 17 7 mM, total base, 151 7 mM

§ Venous pressures of A G made on March 2 were +3 0 cm of water, March 4, +4 5 cm, March 9 +2 5 cm, March 20, +4 0 cm, April 1, +4 0 cm

for obtaining expired air, alveolar air and mixed venous tensions has been described in previous papers.² Arteriovenous differences in carbon dioxide content were obtained by plotting the alveolar and (oxygenated) mixed venous tensions on a carbon dioxide dissociation curve of the patient's blood (venous blood being used in this case). The blood flow was thus determined by the Fick principle. Blood for the serum electrolyte determinations was drawn under basal conditions, these determinations were made by Miss E M Benedict, using the methods described by Atchley and Benedict.³



Changes in the circulatory and respiratory functions of A G (case 3) following pneumothorax. The figures at the top of the diagram indicate the amounts of air injected each time and the date when the injection was given.

In the case of patient F S, the experiments were done under basal conditions. The blood flow determinations also differed from those on patient D R in several other respects: (1) the actual arterial carbon dioxide content was determined by drawing arterial blood (from the brachial artery) shortly after the respiratory

2 Richards, D W, Jr, and Strauss, M L. Circulatory Adjustment in Anemia, *J Clin Investigation* 5 161, 1928, Carbon Dioxide and Oxygen Tensions of the Mixed Venous Blood of Man at Rest, *ibid* 9 475, 1930.

3 Atchley, D W, and Benedict, E M. The Distribution of Electrolytes in Dogs Following Ligation of Both Ureters, *J Biol Chem* 73 1, 1927.

procedure was finished (except in the experiment of January 17), (2) the arterial blood sample was also used for the construction of a point on the oxygenated whole blood carbon dioxide curve, (3) the slope of this curve was not determined experimentally, but was estimated from the oxygen capacity, a justifiable procedure,² especially when, as here, relative and not absolute values are important, (4) a special effort was made to have the oxygenated mixed venous tensions as accurate as possible, two samples being taken at the end of fifteen seconds', and four at the end of twenty seconds', rebreathing in each experiment, the results were good, at least three of the six values being within 0.5 mm of each other in every blood flow determination except the first one (January 10).

Certain minor changes of technic were employed with the third patient, A. G.

- 1 A Tissot spirometer was used to collect expired air instead of a Douglas bag, and the patient breathed outside air in all experiments.
- 2 Alveolar air samples were used in most of the experiments to give arterial blood carbon dioxide values, as the patient had at all times a sufficiently large vital capacity to insure satisfactory alveolar specimens. Arterial blood was also drawn, as a further check on the results, on three occasions, in obtaining these samples, care was taken to have the patient breathing through the mouthpiece and tubing in the same manner as when the expired air and alveolar and venous samples were taken.
- 3 All respiration experiments were done early in the morning under strict basal conditions.
- 4 A carbon dioxide dissociation curve was constructed with one sample of venous blood, and the slope of this curve was used for the determination of arterial and venous blood carbon dioxide contents. As the oxygen capacity of successive blood samples varied little, the use of this slope for all experiments seemed justified.

The residual air values also call for a word of comment. They were calculated from the increase, during rebreathing, in nitrogen percentage in the rebreathed carbon dioxide-oxygen mixture that was used for mixed venous tension determination, such an increase was, of course, due to the nitrogen in the alveolar air. The residual air values so calculated are not exact, but give an approximate estimate of the changes in residual volume that took place during the course of establishment of the pneumothorax.²

The course of pneumothorax production was followed in each patient by repeated fluoroscopic examinations. Dr. Kenneth B. Turner made these examinations.

Venous pressure measurements were made on patient A. G. by a technic essentially that of Moritz and von Tabora.⁴ The figures given for these pressures are in terms of centimeters of water measured from the distal edge of the manubrium sterni.

RESULTS

The finding of particular interest in this study was the consistent and progressive lowering of cardiac output that took place in all three cases as the establishment of unilateral pneumothorax progressed. There was a corresponding increase in the arteriovenous carbon dioxide (and oxygen) differences. The amount of the decrease in volume flow of blood was not great, but was well outside the experimental error of the method. In general, the decrease in blood flow seemed roughly proportional, in

⁴ Moritz, F., and von Tabora, D. Ueber ein Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch f. klin. Med.* 98: 475, 1910.

the three cases, to the degree of collapse of the lung, though the data were not enough to make this indication definite

In the two cases (cases 2 and 3) in which blood studies were made, it will be noted that there was a fairly satisfactory correspondence between alveolar and arterial carbon dioxide values, except in the last arterial blood sample taken on A G (case 3). In this case there was almost certainly an error in the determination of the blood carbon dioxide curve, no obvious break in technic, however, was detected.

In the one case in which it was measured, the venous pressure did not change appreciably during the course of the pneumothorax. The arterial blood pressure showed no consistent variation in any of the three cases. There were no significant alterations in the total oxygen consumption or the carbon dioxide output. The pulmonary ventilation increased only slightly toward the end of the series of air insufflations. The vital capacity and residual air volumes diminished progressively. These observations are consistent with previous work.⁵

Patient D R showed a slight fall in alveolar carbon dioxide tension four hours after a 900 cc pneumothorax injection, F S and A G had, during the time in which they were receiving pneumothorax treatments, a gradual and steady fall in arterial carbon dioxide content and in alveolar and arterial carbon dioxide tensions. This phenomenon was reported several years ago by Meakins and Davies.⁶

In respect to the oxygen saturation of the arterial blood, the results on F S differed from those on A G. As shown in the accompanying table, the former developed a definite, though slight, arterial oxygen unsaturation, while the latter retained his normal arterial saturation percentage, except in the last experiment. Arterial oxygen unsaturation did not occur in any of Meakins and Davies' cases. We have been inclined to associate its occurrences in F S with the rapidity with which the lung collapse was accomplished. Clinically, both F S and A G showed mild but unmistakable cyanosis of the nail beds and lips during the latter part of their course of treatment. The explanation for this in the case of A G, whose arterial saturation was normal, was perhaps the decrease in blood flow, with an increased tissue utilization of oxygen and a decreased venous oxygen content.

5 Means, J H, and Balboni, G M. Respiration in Pneumothorax, *J Exper Med* **24** 671, 1916. Le Blanc, W. Respiratorischer Gasaustausch und Lungen-durchblutung, *Beitr z Klin d Tuberk* **50** 21, 1922. Meakins, J C, and Davies, H W. Respiratory Function in Disease, Edinburgh, Oliver & Boyd, 1925. Myers, J A, and Bailey, W. Vital Capacity Test in Artificial Pneumothorax Therapy, *Am Rev Tuberc* **10** 597, 1925. Anthony and Heine. Spirographische Untersuchungen bei Lungenkollaps, *Beitr z Klin d Tuberk* **71** 362, 1929, **73** 51, 1929.

6 Meakins and Davies (footnote 5)

Fluoroscopic observations showed the usual changes in the lung, mediastinal and diaphragmatic shadows following pneumothorax. Lung collapse was less complete and lung expansion was greater in A G during respiration than in the other two cases, on account of an adhesion between the lung and the wall of the chest. Mediastinal displacement was also less. Patients F S and A G showed a "paradoxical" movement of the diaphragm on the affected side after the later insufflations of air. In all cases, there were lowered mean position and decreased mobility of the diaphragm on the affected side.

There was a delayed but distinct rise in the oxygen capacity of the blood of A G as pneumothorax progressed. This increase was also reported by Meakins and Davies⁶ in their series. The other two patients, D R and F S, were not followed long enough for this change to make itself apparent.

In the serum electrolyte values, which were done on patient D R, twenty-four hours after his first (900 cc) pneumothorax, there seemed to be no changes except for a slight general increase in electrolyte concentrations. The significance of this is not clear.

COMMENT

Much work has been done on the problem of the effect of lung collapse on the volume flow of blood through the lungs in animals. For unilateral pneumothorax experiments, rabbits have been found more satisfactory than dogs, on account of the loose, and often perforate, mediastinum in the latter animal. The best of the earlier work on this subject was that of Bruns.⁷ This investigator found that after closed unilateral pneumothorax in rabbits, the arterial oxygen saturation was normal or nearly so, and he inferred a decreased blood flow through the collapsed, nonfunctioning lung. Bruns also found that collapse of one lung decreased by about 25 per cent the flow of blood perfused through the pulmonary circuit at constant pressure.

Most of the earlier investigations were reviewed and much careful original work was reported in an article published by Weiss⁸ in 1926. After considering all available data, Weiss was able to state definitely that the flow through the collapsed lung, in both open and closed pneumothorax in rabbits, was greatly diminished. The figures on the total blood flow through the pulmonary circuit were somewhat less uniform,

7 Bruns, O. Ueber den respiratorischen Gaswechsel bei Erkrankungen der Lunge, *Deutsches Arch f klin Med* **107** 468, 1912, Ueber die Blutzirkulation in der atelektatischen Lunge, *ibid* **108** 469, 1912.

8 Weiss, R. Ueber die Durchblutung der Kollaps-lunge beim experimentellen Pneumothorax, *Ztschr f d ges exper Med* **53** 138, 1926.

but the great majority of these also showed a decrease following pneumothorax

In man, so far as we are aware, no direct measurement of blood flow before and after pneumothorax has previously been reported. LeBlanc,⁹ however, in three of four cases in which the oxygen contents of arterial and of venous blood were measured, found an increase in the arteriovenous oxygen difference.

If, therefore, a decrease in pulmonary blood flow is the rule following lung collapse, the question arises as to the cause of this phenomenon.

There is the possibility that the increase in intrathoracic pressure following pneumothorax may be a cause of a decreased flow of blood into the thorax. That this factor is not a deciding one, however, is convincingly shown by the recent experiments of Moore.¹⁰ This investigator produced lung collapse in dogs by clamping off one main bronchus, with resulting complete atelectasis of that lung. By this technic the intrathoracic negative pressure would tend to be exaggerated rather than reduced. Of six such experiments in which the left bronchus was tied off, five showed a decreased total blood flow, while all of the seven in which the right bronchus was tied showed a decrease.

Whether the displacement of the mediastinum that occurs with lung collapse may produce embarrassment of the heart action and thus a decrease in the cardiac output is a question on which little evidence is available. If such were the case, one would expect an increase in venous blood pressure. This, however, apparently does not occur to an appreciable extent in man. Of two cases measured, Kroetz¹¹ found one in which the venous pressure increased to about the same extent as the intrathoracic pressure, in other words, the "effective venous pressure" was maintained. In the other case Kroetz found a smaller rise than this in venous pressure. In our case 3, the rise in venous pressure following pneumothorax was insignificant. In experimental pneumothorax, venous pressure changes are apparently a more important factor (Tsunoda¹²).

The chief cause for the decrease in total cardiac output following lung collapse is probably a decrease in the vascular bed and a corresponding increase in resistance in the collapsed lung. The many experiments in animals indicating a marked decrease in blood flow

9 LeBlanc (footnote 5)

10 Moore, R. L. The Volume of Blood Flow Per Minute Through the Lungs Following Collapse of One Lung by Occlusion of Its Bronchus, *Arch Surg* **22** 225 (Feb.) 1931

11 Kroetz, C. Die Koeffizienten des klinisch-messbaren Venendruckes, *Deutsches Arch f klin Med* **139** 325, 1922

12 Tsunoda, H. Ueber die Ursachen der Venendrucksteigerung bei Pneumothorax, *Deutsche Ztschr f Chir* **212** 198, 1928

through the collapsed lung strongly suggest this increase in resistance, the most direct of these experiments are the lung perfusions of the type carried out by Bruns, as quoted. Another phenomenon, noted by Bruns and also by Carlstrom,¹³ that points to an increased resistance in the pulmonary circuit when one lung is collapsed is the hypertrophy of the right ventricle that occurs after long-standing pneumothorax in animals.

If one accepts the statement that the vascular resistance in the collapsed lung is greatly increased, the question arises whether this is due simply to a decrease in size of the vascular bed as a result of the collapse itself, or whether there occurs an active constriction of the pulmonary blood vessels. The perfusion experiments of Bruns, which were carried out on animals' lungs during the half hour immediately after the death of the animal, suggest the former. Other work has confirmed the finding of a progressive decrease in flow through the perfused lung when it is reduced from the expanded to the collapsed state, Daly's¹⁴ recent experiments show this clearly. Further evidence in the same direction is offered by the interesting work of Coryllos and Birnbaum.¹⁵ These investigators found that when iodized oil was injected into the jugular vein of a dog with unilateral lung collapse, the oil particles were of such size that they were caught in the smaller branches of the pulmonary artery. They noted further that the oil particles were distributed about equally between the collapsed and the normal lung. When, however, india ink was similarly injected, the particles penetrated to the pulmonary capillaries, and it was found that the capillaries of the collapsed lung contained considerably less of the particles than those of the normal lung. The authors interpreted this as indicating that the capillaries or alveolar blood vessels were the elements of the pulmonary circuit which were constricted by lung collapse.

The degree to which the flow through the collapsed lung will be reduced, as compared with that through the normal lung, thus depends on the relative resistances along these two parallel circuits. This phase of the problem has been well discussed by Weiss.⁸

There remains the possibility of nonmechanical, vasomotor changes in the pulmonary blood vessels following pneumothorax. On this point we have not found evidence in the literature.

It is perhaps worth noting that if a decreased blood flow is actually the rule after artificial pneumothorax, this phenomenon may well be

13 Carlstrom, P. G. Beitrag zur Frage der Wirkung des kunstlichen Pneumothorax auf Herz und Zirkulation, Beitr. z. Klin. d. Tuberk. **22** 243, 1912.

14 Daly, I. de B. Resistance of the Pulmonary Vascular Bed, J. Physiol. **69** 238, 1930.

15 Coryllos, P. N., and Birnbaum, G. L. The Circulation in the Compressed, Atelectatic and Pneumonic Lung, Arch. Surg. **19** 1346 (Dec.) 1929.

associated with the gradual steady increase in the red blood count and hemoglobin that has been shown to occur¹⁶

A further consideration, which so far as we know has not been stressed before, is the fact that this decrease in cardiac output with an increase in peripheral (pulmonary) resistance appears to contradict Starling's "law of the heart," according to which the heart puts out the same volume of blood in spite of wide variations in arterial resistance, providing the venous inflow is constant. Whether there is actually a contradiction here of the law of the heart or whether alterations in venous return, or other circulatory function, are a more immediate cause for the decreased cardiac output is a question that cannot be discussed further with the data available in the present investigation.

Finally, the progressive fall in blood carbon dioxide levels, which occurred in F S and A G, requires explanation. Meakins and Davies,⁹ in discussing this phenomenon in their series of cases, brought evidence to show that the carbon dioxide change was associated with the improved pulmonary function that followed the clearing of the infiltrative tuberculous process. In other words, the original carbon dioxide level was high and gradually returned toward normal as the condition of the lung improved. In the case of our two patients, however, this explanation is not satisfactory. 1 There was no carbon dioxide "retention," in the sense that carbon dioxide levels at the beginning were well within normal limits. The arterial serum p_H was also normal. 2 The tuberculous process in the lungs was not very extensive. 3 This process did not show any signs of clearing during the period of observation. 4 The vital capacity and the residual air were both progressively decreasing during the period of observation.

It is of interest to consider the fall of carbon dioxide levels in relation to some of the other changes that have been shown to occur following pneumothorax. As noted, both the vital capacity and the residual air are decreased. More significant than these values, however, from the point of view of the respiratory exchange, is the fact that the "normal capacity" (the volume of air in the lungs at the end of a normal respiration) is also diminished (Anthony and Heine¹⁷). With a smaller mean lung volume, and the same (or slightly increased) pulmonary ventilation, one would expect a more complete washing out of the alveolar spaces with each respiration and therefore (other things being equal) a lower alveolar carbon dioxide tension and a higher oxygen tension in the alveolar air. If alveolar and arterial carbon dioxide tensions are nearly the same, as they are under normal conditions, it follows that the arterial carbon dioxide content will also be reduced. The state of the

16 Meakins and Davies (footnote 5) Bruns (footnote 7)

17 Anthony and Heine (footnote 5)

circulation, however, is not the same the total blood flow through the lungs is reduced, and the blood is presumably flowing through a smaller capillary bed The latter state, in particular, will make proper gas exchange in the lungs more difficult Whether a decreased circulation rate through the lungs increases or diminishes the efficiency of oxygen and carbon dioxide exchange is not known the greater time of flow through pulmonary capillaries will provide for a closer equilibrium between blood and lung gases, on the other hand, the pulmonary artery blood will be more "venous" and so require a larger gas exchange for proper arterialization

In point of fact, the change in pulmonary circulation did not appear to disturb the close equilibrium that exists between alveolar and arterial carbon dioxide tensions, with the result that both alveolar and arterial carbon dioxide levels (owing to more efficient alveolar ventilation) were decreased

The situation was not the same with regard to oxygen transport in the lungs The tendency to arterial oxygen unsaturation indicates that in respect to this gas, the pulmonary function was below normal The difference between the efficiency of carbon dioxide transport and of oxygen transport was very possibly due to the different diffusion rates of these gases through the alveolar membranes The greater engorgement of the capillary blood vessels in the actively functioning regions of the lungs would be expected to hinder the proper oxygenation of the blood It is possible also that the arterial unsaturation was due in part to blood flowing through unaerated, or poorly aerated, channels in the lungs Since, however, other investigators have found normal oxygen saturations after pneumothorax, the effects of the foregoing factors must be quite variable in different cases

In brief, then, the situation existing after pneumothorax in our cases was one of increased efficiency in carbon dioxide transport by the lungs, together with decreased efficiency in oxygen transport

From the point of view of the respiratory stimulus, it is interesting that the same, or slightly increased, pulmonary ventilation is maintained in spite of lower arterial carbon dioxide tension and even in one case of increased arterial p_H The situation here is probably not unlike that described by Kroetz¹⁸ in a certain stage of early cardiac decompensation, in which lowered carbon dioxide tension and increased arterial p_H indicated an uncompensated alkalosis As Kroetz pointed out, there existed in these cases a definitely decreased arterial oxygen tension, though the percentage of saturation was normal A similar situation apparently existed in A G (case 3), F S (case 2) had an actual arterial anoxemia

18 Kroetz, C Formen der Dyspnoe I Kardiale Dyspnoe, Deutsches Arch f klin Med 169 257, 1930

SUMMARY

1 Studies of the cardiac output and other functions of the circulation have been made before and after artificial pneumothorax in three cases of pulmonary tuberculosis

2 The cardiac output was decreased following pneumothorax in all cases. Among the other changes that occurred were decreased vital capacity and residual air and lowered alveolar and blood carbon dioxide levels. The interrelations of some of these changes are discussed

REPORT OF CASES

CASE 1—*History*—D. R. (no 80552), a boy, aged 17, was first admitted to Bellevue Hospital on Aug. 28, 1928, with a five months' history of cough and night sweats and a loss of 10 pounds (4.5 Kg.) in weight.

Examination—Examination at this time showed signs of infiltration throughout the upper lobe of the left lung. The sputum was positive for tubercle bacilli. During the next four months, he improved clinically, but the process in the lungs extended somewhat and a cavity formed at the apex of the left lung. His weight in September, 1928, was 118 pounds (53.5 Kg.), and on March 16, 1929, was 132 pounds (59.9 Kg.). He was transferred to the Presbyterian Hospital on March 20.

Examination of the blood showed hemoglobin, 82 per cent (Sahli), red cells, 4,670,000, white cells, 14,500, polymorphonuclears, 66 per cent, lymphocytes, 29 per cent, monocytes, 4 per cent, basophils, 1 per cent. The urine was normal.

An electrocardiogram gave normal tracings. A roentgenogram showed infiltration extending into the apexes of both lungs, with a cavity in the left.

Course—The patient was comfortable and practically free from symptoms throughout his stay, except for those due to pneumothorax. Nine hundred cubic centimeters of air was injected by Dr. Amberson on April 1, following which the pulse rate rose to 120, and there were dyspnea and a transient cyanosis lasting about two hours. The second and third insufflations were followed by tachycardia and an increased respiratory rate, but no cyanosis. Roentgenograms and fluoroscopy showed no evidence of adhesions of the left lung to the chest wall. The heart was markedly displaced to the right. The patient was transferred to Bellevue Hospital on April 9.

CASE 2—*History*—F. S. (no 239168), a white man, aged 24, was admitted to the hospital on Dec. 30, 1929, complaining of cough, transient pains in the right side of the chest and loss of weight for five months. He had had a few night sweats. He had lost 25 pounds (11.3 Kg.), and the present weight was 105 pounds (47.6 Kg.). He had been at Bellevue Hospital for seven weeks before admission, where moderate tuberculous infiltration and excavation had been found. A week before, he had received a small artificial pneumothorax (150 cc.).

Examination—Examination showed a pale, undernourished young man with a frequent cough of varying severity, bringing up mucopurulent sputum. The trachea was in the midline. There were deep supraclavicular fossae. The lung expansion was good, the chest was symmetrical. There was dulness over the right apex, with bronchovesicular breath sounds and many moist râles after coughing. The heart was normal, the apex was 8 cm. to the left in the fifth space. The blood pressure was 95 systolic and 70 diastolic.

Examination of the blood showed hemoglobin, 89 per cent (Sahli), red cells, 4,500,000, white cells, 10,280, polymorphonuclears, 73 per cent, lymphocytes, 21 per cent, monocytes, 5 per cent, eosinophils, 1 per cent. The red cells showed central pallor. The sputum contained tubercle bacilli on several occasions.

A roentgenogram of the chest taken Dec 30, 1929, showed a dense process through the upper lobe of the right lung, with a large cavity 3 cm in diameter in the right infraclavicular region. The diaphragm appeared normal.

Course—During the patient's stay of one month in the hospital, he had a low fever most of the time, about 100 F, during the week from Jan 9 to 15, 1930, the afternoon rise was as high as from 101 to 102 F. He was relatively comfortable, he was bothered at times by coughing in the night, he had an irregular appetite, and there was a good deal of diaphoresis. Following the first pneumothorax, on January 21, there was a transient rise of the pulse rate to 130 and slight dyspnea, which subsided in a few hours. There was a mild cyanosis of the nail beds, which nearly cleared after two days. Subjectively, the patient had a sensation of tightness in his chest. The symptoms after the succeeding injections of air were similar but less marked, except that cyanosis of the nail beds persisted, the respiration became shallow and slightly increased in rate, and he noticed his heart beating against the chest wall on the left side. On January 28, the right border of cardiac dulness in the fourth space was 3.5 cm to the left of the midline. It was observed that after slight exertion the patient became more cyanosed. Roentgen examination of the chest on January 27 showed the right lung to be collapsing freely, except for adhesions just beneath the clavicle. Fluoroscopy showed that the collapsed lung did not move appreciably with respiration. The patient was transferred back to Bellevue Hospital on February 1.

CASE 3—History—A. G. (no 287218), a Russian-born Jewish boy, aged 20, was admitted to the hospital on Feb 17, 1931, complaining of cough, hemoptyses and loss of weight during the preceding five months. He had worked as a shoe salesman for the past three years, being in a poorly lighted, damp basement. A brother had active tuberculosis. There had been no important previous illnesses.

Five months before admission, he caught a severe chest cold, cough developed, with sputum that became blood-streaked. The patient was in Queensboro Hospital for two weeks, a roentgenogram taken there was negative. He went home and rested for three weeks, and then returned to work. He soon lost his appetite, and his weight dropped from 132 to 117 pounds (59.9 to 53.1 Kg). Nine weeks before admission, the cough returned and he had two hemoptyses of from 100 to 200 cc. The sputum increased, and he had night sweats. He stayed in bed at home for a month, and then went to Bellevue Hospital. A moderately advanced exudative tuberculous lesion was found in the left lung above the third rib. On February 14, a small pneumothorax of 150 cc was given on the right side. The patient was then transferred to the Presbyterian Hospital for study.

Examination—Examination showed a somewhat undernourished Jewish boy who appeared chronically, but not seriously, ill. The lungs showed dulness, diminished breath sounds and increased whispered voice over the upper lobe of the right lung posteriorly, and below the clavicle anteriorly. There were moist râles in this region.

Examination of the blood showed hemoglobin, 78 per cent, red cells, 4,920,000, white cells, 14,600, polymorphonuclears, 78 per cent, Wassermann reaction, negative. Urinalysis gave negative results. Tubercle bacilli were found in two of four sputum examinations.

Roentgenograms of the chest showed mottled infiltration involving the apex of the right lung and the first and second interspaces. Subsequent roentgenograms showed the production of a partial pneumothorax, with adhesion to the chest wall at the level of the second interspace. A small (1.5 cm) cavity in this region was visualized. A little fluid collected in the costovertebral angle.

Course—The patient's general condition remained about the same. He had a low fever at times. Pneumothorax was started on March 4 and was given twice a week, 4,750 cc of air being injected in the course of five weeks. The pulse rate increased, the pulmonary ventilation increased slightly, and the vital capacity fell from 4,100 to 3,100 cc during this time. Fluoroscopy showed partial collapse, but the lung still moved somewhat during quiet respiration. Subjectively, the patient felt fairly well, there was no pain in the chest.

The patient had a small intestinal hemorrhage (hemorrhoids?) on March 20. On March 30, he had some discomfort in the right ear, he was found to have a low grade infection of the middle ear and maxillary sinusitis. He was transferred to Bellevue Hospital again on April 8, 1931.

PANCREATIC EXTRACT IN THE TREATMENT OF ANGINA PECTORIS AND INTERMITTENT CLAUDICATION

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AND

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Much experimental and pathologic evidence has accumulated to indicate that the pain of angina pectoris is due to disturbance of the coronary circulation. The ideal therapeutic measure, then, would be one that insures at all times an adequate flow through the coronary arteries. Of the various drugs used in the treatment of this disease, those which are known to dilate the coronary arteries have received the widest acceptance. For relief from the attack, the nitrites are invaluable, not only because they reduce the systemic blood pressure and thus relieve in part the burden imposed on the heart muscle, but also because in all probability they decrease myocardial ischemia. Unfortunately, their effect is transitory. For the prevention of attacks, another class of drugs which act in much the same manner, namely, the purine derivatives (theobromine, theophylline, etc.) have proved of value. However, these drugs fall short of the ideal because they are often badly borne by the patient and because a tolerance to them is quickly acquired.

In this paper we wish to summarize our experience with a new preparation, an insulin-free extract of the pancreas. It is well tolerated in large doses. It is an active coronary dilator with a prolonged effect. In many instances it will prevent attacks of angina pectoris that recur after the usual methods of treatment. We have furthermore found it superior to other measures in the treatment of intermittent claudication.

It was originally noted,¹ several years ago, that the pain of angina pectoris was sometimes relieved by insulin in diabetic patients with this syndrome. The degree of relief was apparently not dependent on the amount of insulin used. It remained for Gley and Kisthimos² to

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1 Heteny and Budinger, cited by Vaquez, Giroux and Kisthimos, *Presse med* **37** 1277 (Oct 2) 1929

2 Gley, P, and Kisthimos, N. *Recherches sur la substance hypotensive de pancréas*, *Presse méd* **37** 1279 (Oct 2) 1929

demonstrate that the effective material was not insulin, but another substance present in the pancreas. They succeeded in making an insulin-free pancreatic extract, which Vaquez³ used in the treatment of angina pectoris and spastic obliterative arterial disease with remarkable results. In 1929 he reported a series of twenty cases of severe anginoid seizures in which from partial to complete amelioration of symptoms resulted from the treatment in almost every instance. Similar results were obtained in the treatment of intermittent claudication. The duration of relief was variable, but in several instances no symptoms recurred after prolonged observation. He concluded that this therapy was far superior to any surgical measure.

Wolffe and his co-workers,⁴ in this country reported similarly favorable results from this method of treatment. In a series of twenty instances, complete relief from anginoid seizures was obtained in 55 per cent, 30 per cent of the patients were partially relieved, and three, or 15 per cent, experienced no relief. Two of the latter showed decompensation at the time that treatment was given, as the author remarked, Vaquez had observed complete failure in such instances.

PHARMACOLOGIC PROPERTIES

Pharmacologic studies, together with the method of preparation of the extract, have been reported elsewhere.⁵ The pertinent observations may be summarized at this time.

The pancreatic extract, on intravenous injection into the rabbit, causes a transitory hypotension which is not the result of cardiac slowing and is not due to peptones, choline or histamine. The "hypotensive unit," as defined by Gley and Kisthinos, has been adopted. It is that amount of the extract injected intravenously which is sufficient to cause a barely perceptible fall in the blood pressure of a rabbit weighing 2 Kg. Repeated injection of the unit dose, or continuous intravenous perfusion in an approximate dose of 0.002 hypotensive unit per kilogram per minute may result in a prolonged hypotension from cumulative action. The extract causes vasoconstriction of the vessels of a perfused rabbit's leg, hence the hypotension is probably due to splanchnic vasodilatation.

3 Vaquez, H., Giroux, R., and Kisthinos, N. De l'action de certains extraits pancreatique dans le traitement de l'angine de poitrine, *Presse med* **37** 1277 (Oct 2) 1929.

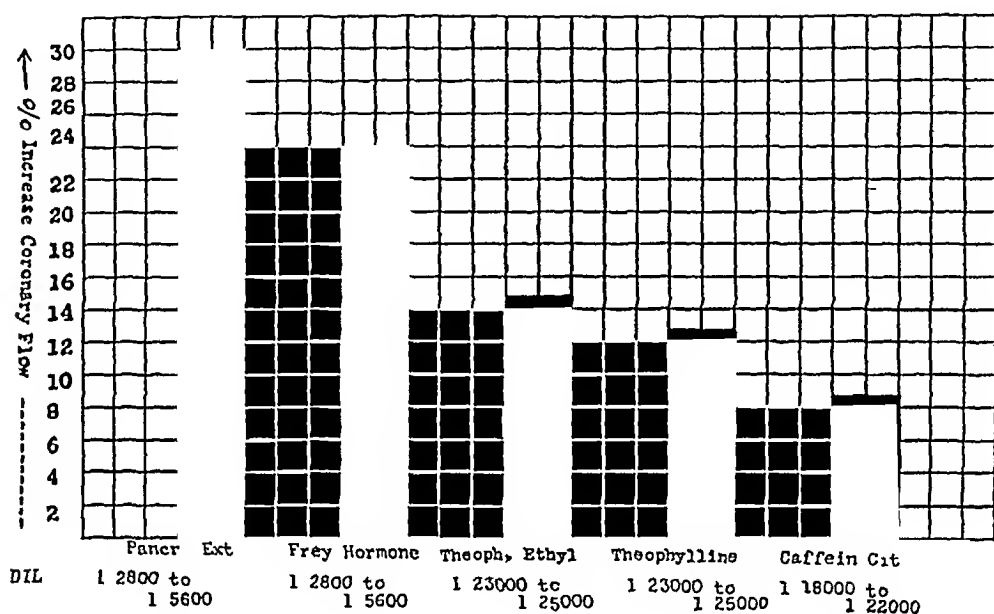
4 Wolffe, J. B., Findlay, D., and Dessen, E. Treatment of Angina Pectoris with a Tissue Vasodilator Extract, *Ann Int Med* **5** 625 (Nov) 1931.

5 Elliot, A. H., and Nuzum, F. R. The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulatory Hormone of Frey, *J Pharmacol & Exper Therap* **43** 463 (Nov) 1931.

The pressor effect of epinephrine may be modified or abolished by the extract. As noted by its elaborators, the extract protects the experimental animal from lethal doses of epinephrine. It does not, however, modify the action of epinephrine on the carbohydrate metabolism, it modifies only its action on smooth muscle.

None of these effects was obtained after subcutaneous or intramuscular injection of the extract.

Using the perfused rabbit's heart, we found that the extract in dilutions corresponding to the therapeutic dose in man is an active coronary dilator. The degree of coronary dilatation exceeded by one-half that obtained with the most active of the purine group in this respect, theophylline ethylenediamine.



Effect of pancreatic extract, Frey hormone, theophylline ethylenediamine, theophylline and citrated caffeine on the coronary flow of the perfused rabbit's heart. The vertical scale at the left indicates the increase in coronary flow in per cent.

The results are expressed graphically in the accompanying chart. The height of each column indicates the average increase in coronary flow as determined in from five to ten experiments conducted over a period of ten minutes on fresh hearts. Pancreatic extract caused an average increase of 30 per cent, the Frey "hormone," as prepared from the urine, an increase of 24 per cent. The purine derivatives, theophylline ethylenediamine, theophylline and caffeine, were less effective, producing increases of 15 per cent, 13 per cent and 9 per cent, respectively.

The effects of the intravenous injection of the extract into man were studied in a few instances. With a dosage of 30 hypotensive units, patients with hypertension experienced an immediate transitory, "nitrite"

reaction (flushing of the face, vertigo, faintness and palpitation) and a pronounced fall of systolic blood pressure, together with tachycardia which persisted for about one hour. No changes were apparent in the electrocardiogram taken during and following the injection. In persons with normal blood pressure, little or no effect was noted. Although no untoward reactions occurred, the number of these observations was limited. It is not recommended that the extract be given intravenously without further study.

NATURE OF THE ACTIVE PRINCIPLE

The exact nature of the active principle remains obscure. Because of similarity in physiologic properties, Wolffe suggested that we might be dealing with an adenine compound. Drury and Szent-Gyorgyi⁶ and Wedd⁷ recently studied the properties of a substance prepared from extracts of heart muscle and identified as an adenine compound, probably adenylic acid. Among other effects, adenylic acid and related compounds cause a transitory fall in blood pressure in the experimental animal, an increase in the coronary flow of the perfused rabbit's heart exceeding that produced by sodium nitrite and theophylline and transitory complete heart-block in the guinea-pig. The latter effect is regarded as specific for these compounds. We have been unable to produce it.

Another principle regarded as a hormone, and having closely allied with the pancreatic extract, and so are doubtful of the identity of these principles

properties, has been described. Frey and his co-workers⁸ isolated in fairly pure form a substance present in the urine of normal persons and animals that on intravenous injection into the dog causes hypotension

6 Drury, A. M., and Szent-Gyorgyi. Physiological Activity of Adenine Compounds with Special Reference to Their Action on the Mammalian Heart, *J. Physiol.* **68** 213 (Nov.) 1929.

7 Wedd, A. M. The Action of Adenosine and Certain Related Compounds on the Coronary Flow of the Perfused Heart of the Rabbit, *J. Pharmacol. & Exper. Therap.* **41** 355 (March) 1931.

8 Frey, E. K., and Kraut, H. Ein neues Kreislaufhormon und seine Wirkung, *Arch. f. exper. Path. u. Pharmacol.* **133** 1, 1928. Kraut, H., Frey, E. K., and Bauer, E. Ueber ein neues Kreislaufhormon, *Ztschr. f. phys. Chem.* **175** 97, 1928. Frey, E. K., and Kraut, H. Nachweis und Wirkung eines Kreislaufhormon, *Munchen med. Wchnschr.* **75** 763 (May 4) 1928. Frey, E. K. Kreislaufhormon und innere Sekretion, *Munchen med. Wchnschr.* **76** 1951 (Nov. 22) 1929. Kraut, H., Frey, E. K., and Werle, E. Der Nachweis eines Kreislaufhormon in der Pankreasdruse, *Ztschr. f. phys. Chem.* **189** 97, 1930. Frey, E. K. A New Internal Secretion of the Pancreas, quoted in *Foreign Letters*, *J. A. M. A.* **95** 676 (Aug. 30) 1930. Frey, E. K., Kraut, H., and Schultz, F. Ueber eine neue innersekretorische Funktion der Pankreas, *Arch. f. exper. Path. u. Pharmacol.* **158** 334, 1930.

and an increase in cardiac rate and amplitude of contraction. This substance is present in the blood stream in combination with an inactivator from which it may be liberated. Frey believes that it is present in most organ extracts but is probably elaborated by the pancreas, because after experimental pancreatectomy the rate of urinary excretion is decreased 80 per cent or more. The linkage between the hormone and inactivator depends on the reaction of the tissues, so that the appearance of "acid metabolism" releases a portion of the hormone, resulting in its vasodilator action.

The hormone has been used clinically with, for the most part, favorable results. Frey stated that as the result of its use he has seen lowering of the blood pressure in essential hypertension, cessation of attacks of angina pectoris and intermittent claudication and avoidance of amputation in gangrene of the extremities resulting from arterial disease. Leschke,⁹ using this preparation, obtained gratifying results in all manner of angiospastic syndromes including angina pectoris, and believes that it is the treatment of choice in arteriosclerotic gangrene and thrombo-angitis obliterans. He obtained identical results with the insulin-free pancreatic extract. Schauder¹⁰ described a patient with severe intermittent claudication of a year's duration who, as the result of treatment with the hormone, had remained entirely symptomless following treatment for a period of thirteen months. The patient also had hypertension, and a pronounced and lasting fall in blood pressure resulted.

On the other hand, Singer¹¹ had no success with either the "circulatory hormone" or the pancreatic extract in these conditions, and attributed the favorable results reported by others to a nonspecific protein effect.

Extracts of other tissues, namely, heart, liver and skeletal muscle, have been found to exert a beneficial effect on the anginal syndrome. Haberlandt,¹² in 1924, found that an extract made from the cardiac conduction system had the ability of initiating and regulating the beat of an isolated heart perfused with it. He believed it to be a "heart hormone." Salomon and Zuelzer¹³ found a similar principle in an

9 Leschke, E. Erfahrungen mit dem Kreislaufhormon "Kallikrein," *Munchen med Wchnschr* **77** 1167 (June 22) 1930.

10 Schauder, H. Zur Behandlung der intermittierenden Hinkens, *Munchen med Wchnschr* **77** 485 (March 21) 1930.

11 Singer, R. Die praktischen Ergebnisse der "Herz Hormon" Therapie, *Wien klin Wchnschr* **46** 39 (Jan 9) 1931.

12 Haberlandt, L. Ueber das Herzhormon, *Endokrinologie* **6** 335 (May) 1930.

13 Salomon, H., and Zuelzer, G. Ueber das aus der Leber gewonnene Herzhormon "Eutonon," *Ztschr f d ges exper Med* **66** 291, 1929.

extract of liver These two preparations, together with a skeletal muscle extract introduced by Schwarzmänn,¹⁴ are regarded by their elaborators as of distinct benefit in the treatment for angina pectoris Haberlandt believes that the skeletal muscle extract of Schwarzmänn contains a substance identical with his "heart hormone" Fahrenkamp and Schneider¹⁵ came to a similar conclusion They compared the effects of these two preparations on patients with angina pectoris The results were identical, the angina being favorably influenced

We have not had the opportunity of studying these preparations However, in conjunction with the studies on the pharmacology of the pancreatic extract, we conducted parallel observations on the "circulatory hormone" of Frey as prepared from the urine It was found to have similar vasodilator properties, and, in addition, it modifies the pressor effects of epinephrine and is an active coronary dilator On the strength of these observations, it may be concluded that these two preparations probably contain the same active principle

From this review it is evident that a substance or substances have been found in various animal tissues and fluids that have similar physiologic properties Whether the active principles are identical or represent a class of substances or a hormone is not known at this time It is striking, however, that these investigators, working independently, have observed a salutary influence exerted by their preparations on the symptoms and course of spastic and obliterative arterial disease as typified by angina pectoris, intermittent claudication, arterial hypertension and trophic disturbances of the extremities

CLINICAL STUDIES

Dosage—We administered the extract intramuscularly in doses of from 30 to 60 hypotensive units on alternate days or twice weekly, depending on the severity of the symptoms, for a total of from ten to twelve doses This procedure was followed in both angina pectoris and intermittent claudication If amelioration of symptoms was not apparent after such a course, the injections were repeated after a week's interval In refractory cases, a third such course was given before it was concluded that the treatment was without avail Frequently, anginal attacks ceased after from four to five injections If symptoms recurred after weeks or months, the treatment was repeated if possible Toxic symptoms or side reactions were not noted during or after repeated

14 Schwarzmänn, J S Ein neuer Weg in der Therapie der Angina pectoris, München med Wchnschr 76 1329 (Aug 9) 1929

15 Fahrenkamp, K, and Schneider, H Vergleichende Untersuchungen mit einem als "Hormocardiol" bezeichneten Herzhormonpräparat und einem neuartigen Muskelextrakt, Med Klin 26 48 (Jan 10) 1930

series of injections Burning and slight induration were often encountered at the site of injection

Careful attention has been paid to the potency of the material used During the early months we prepared our own extract Later it was supplied by two commercial houses Each lot was tested on the rabbit and the dosage was determined on that basis We also tested material on the perfused heart to assure ourselves that the coronary dilator principle was active Frequently a discrepancy was encountered between this and the vasodilator property of the extract This may have been due to a trace of choline or histamine, which are coronary constrictors Only that material was used which actively dilated the coronary arteries

Selection of Cases—Three groups of patients were studied The first group comprised forty-one persons with angina pectoris who received the usual treatment, namely, limitation of activity, the use of nitrites and nitroglycerin when effective and various combinations of the purine derivatives, together with such drugs as phenobarbital, atropine, a mixture of opium alkaloids, etc A diminution of tobacco consumption was insisted on This group served as a control

The second series consisted of twenty patients with angina treated with the pancreatic extract Many of these had previously had the benefit of other methods of therapy

The third group numbered five persons with intermittent claudication and two with other types of arterial disease

All of these patients were seen in private practice No attempt at selection was made beyond the reasonable certainty of diagnosis and the elimination of patients with coronary thrombosis Patients with syphilitic aortitis were not excluded, as Vaquez had obtained relief with the treatment in such instances Orthodiagraphic heart measurements and electrocardiograms were made on each patient The follow-up period was of sufficient length to admit of accurate evaluation of the therapeutic measures employed

For purposes of comparison, the control and treated groups of angina patients were divided into three subgroups each, depending on the severity of the disease As the criteria for this division, the limitation of physical and emotional activity and the duration and severity of the attacks were considered

The control group was followed for an average period of twenty and four-tenths months Nineteen patients had hypertrophied hearts, as determined by the orthodiagram, and twelve of these had hypertension Definite electrocardiographic evidence of myocardial damage was present in thirteen, or 31.7 per cent, of the group The urinalyses gave uniformly negative results Two positive Wassermann reactions were encountered in the group The first patient had a syphilitic aortitis

and received pronounced benefit from antisyphilitic medication. The second patient, 70 years of age, had a 2 plus Wassermann reaction of the blood, and was helped by potassium iodide. The duration of symptoms varied from one week to one hundred and eighty months at the time that treatment was instituted, averaging twenty-four and four-tenths months.

Results of Treatment—The salient facts are presented in table 1. Three of these patients were classified as having slight attacks, one of them received no relief from treatment, one was moderately benefited, and one markedly relieved. Of the twenty patients with attacks of moderate severity, four experienced no relief, seven were moderately benefited and nine showed pronounced improvement. Eighteen patients had a severe form of the disease. Five of these were unrelieved by

TABLE 1—*Results in Forty-One Patients with Angina Pectoris, Treated by the Usual Measures*

Severity of Attacks	Num ber of Cases	Duration of Symptoms	Aver age Time Ob served,	Coronary Disease (Electro cardio gram)		Degree of Relief							
						None		Moderate		Marked		Died	
				No	%	No	%	No	%	No	%	No	%
				Mo									
Slight	3	1 wk to 17 mo (av 5 mo)	17 6	1	33	1	33	1	33	1	33		
Moderate	20	3 to 144 mo (av 36 4 mo)	20 9	6	30	4	20	7	35	9	45		
Severe	18	1 wk to 180 mo (av 32 mo)	22 8	6	33	5	27 7	6	33	4	22 2	3	16 6
Totals	41	Av 24 4 mo	20 4	13	31 7	10	24 3	14	34 1	14	34 1	3	7 4

treatment. Six were somewhat relieved and four were benefited greatly. Three of the eighteen patients died during the period of observation.

In summary, of the total group of forty-one control patients, ten, or 24.3 per cent, were not helped by treatment, fourteen, or 34.1 per cent, experienced moderate relief, and fourteen, or 31.7 per cent, received pronounced benefit. Three patients, or 7.4 per cent, died during observation.

The group of twenty patients treated with pancreatic extract presents a similar cross-section. Eleven had hypertrophied hearts, and there was electrocardiographic evidence of myocardial damage in twelve, or 60 per cent. Ten had hypertension, of whom one had a mild diabetes mellitus and one a chronic nephritis. No evidence of syphilis was encountered in this group.

The duration of symptoms when first seen (average, twenty-three and three-tenths months) was similar to that in the control group, varying from one week to eight years. At least 50 per cent of these patients

had been treated by the usual methods without appreciable benefit before the extract was given. This enhances the significance of the satisfactory results obtained in these instances.

Each patient received from 120 to 1,140 hypotensive units (average for the group, 517.5 units). During the treatment with the extract, other methods of therapy previously instituted were, in most instances, interrupted. A few patients continued to take vasodilator drugs for relief from attacks during the time that the first few injections of the extract were administered. After the completion of the course these drugs were stopped, except in two instances in which the extract was ineffective. Every patient has been followed to the present time. The shortest period of observation following treatment was one month, the longest twenty-two months and the average for the group nine and five-tenths months.

TABLE 2—Results in Twenty Patients Treated with Pancreatic Extract

Severity of Attacks	Num ber of Cases	Duration of Symptoms	Aver age Time Ob served, Mo	Coronary Disease (Electro cardio gram)		Number Hypo tensive Units Given	Degree of Relief							
				No	%		None		Moder ate		Marked		Died	
							No	%	No	%	No	%	No	%
Slight	2	1 wk , 18 mo	14 0			120, 585 (av 352)			1	50	1	50		
Moderate	8	1 to 48 mo (av 20 3 mo)	13 0	5	62 5	100 to 570 (av 362 5)	1	12 5	3	37 5	4	50		
Severe	10	1 5 to 96 mo (av 31 7 mo)	24 2	7	70	210 to 1,140 (av 838 0)	1	10 0	1	10 0	6	60	2	20 0
Totals	20	Av 23 3 mo	17 0	12	60	Av 517 5	2	10 0	5	25 0	11	55	2	10 0

The results of treatment are given in table 2. Two of the twenty patients were considered as having attacks of mild severity. One of these was moderately helped, and the other received pronounced benefit. The attacks were moderately severe in eight patients, and five of these had electrocardiographic signs of myocardial damage. In one the attacks proved refractory, three were moderately helped by the extract and four were almost entirely relieved.

The group of ten patients with severe angina is of particular interest. Seven of them had pronounced myocardial damage as evidenced by the electrocardiographic tracings. Their average duration of symptoms was thirty-one and seven-tenths months at the time that treatment was instituted, and they received an average of 838 units each. One patient was not benefited, one was moderately improved and six showed pronounced benefit. Two patients of this group treated with pancreatic extract died suddenly during observation. Necropsy was not possible, but coronary occlusion was suspected. One of these patients, a woman aged 54, while in the hospital had repeated severe nocturnal attacks of

angina pectoris and cardiac asthma, these were so benefited by the extract that she was able to return to her household duties without further precordial distress until death supervened four months later. The other patient, a man aged 71, who had hypertension and diabetes mellitus, when first seen could not walk two blocks without precordial oppression. He was symptomatically relieved after twelve injections until death four months later.

Two patients were not helped by the extract. One had congestive heart failure at the time that treatment was given. Vaquez and Wolffe have likewise experienced failure under these circumstances. The other patient, a man aged 65, who had a blood pressure of 210 systolic and 90 diastolic and a severe angina of six weeks' duration, was unimproved after 1,080 units and rest in bed for one month.

Of the twenty patients, then, two (10 per cent) were not helped, five (25 per cent) were somewhat relieved and eleven (55 per cent) were greatly helped, while two, who experienced benefit from the treatment, died.

The duration of the benefit received from the injections is difficult of evaluation. As mentioned, all of the patients have been followed to the present time. The treated group has fared decidedly better than the control group. We do not wish to ascribe this result entirely to this method of treatment. A necessary part of the program has been to teach the patient to adjust his life to the restrictions imposed on his activity by his disease so that he may be enabled, so far as possible, to avoid those things which precipitate an anginal seizure. However, the patients in the control series received fully as much consideration in this regard, yet the improvement has not been so lasting as that of the treated group. It is possible that our facility in the general management of patients with angina may have improved since we treated the control group of patients, but it seems unlikely that this factor is in itself sufficient to explain the results obtained in the group receiving the pancreatic extract.

The blood pressure was not significantly altered in the patients with hypertension. Kervarec and Enachesco¹⁶ reported favorable results in fifty-two patients with hypertension treated with the extract. Lowering of blood pressure, particularly in instances of essential hypertension, became evident after three or four injections and persisted for as long as seven months. We were unable to confirm these results.

Intermittent Claudication—Five patients with this syndrome have been treated with the extract. The same dosage was used as in the treatment for angina pectoris. The results have been exceedingly

¹⁶ Kervarec and Enachesco. The Effect of Insulin-Free Pancreas Extract in Arterial Hypertension, *Progres med* 58 194, 1930.

gratifying. No case has proved entirely refractory. One of these patients also had angina pectoris. Following a course of 1,140 units, the anginal attacks materially lessened in number and severity, and the patient was able to walk comfortably four times as far as he could previous to treatment.

Three of these patients had calcareous changes in the leg vessels as shown by roentgenograms. One had discoloration and burning of the feet and extreme pain in the calves on walking. This patient was so improved after 140 hypotensive units that he returned to his work as janitor. The cyanosis of the feet was not influenced, however. The most satisfactory result was obtained in a patient, 76 years of age, who could not walk one block without pain in the legs. Following a course of 900 units, he could walk for two miles without discomfort. This improvement has been maintained over a three months' period.

One patient with an early thrombo-angitis obliterans of the extremities was studied. A Mexican, aged 39, when first seen was wearing felt pads in his shoes because of almost constant pain and tenderness in the balls of the toes, which at times extended into the calves of the legs. Sleep was impossible because of the pain, and the patient was exhausted. He used tobacco to excess. Nothing of moment was found on examination except pallor of the toes. No arterial changes were evident in the roentgenogram. After a course of 330 hypotensive units the patient slept the night through and could walk twelve blocks without distress. The color of the toes was improved.

Another patient, 87 years of age, with generalized arteriosclerosis but a normal blood pressure, had mild, intermittent attacks of precordial distress, and on two occasions repeated attacks of numbness and tingling of the right arm and right side of the face, unilateral muscular weakness and difficulty of speech. On the first occasion the symptoms disappeared following five injections of the extract. They recurred six months later. The extract was immediately administered, and the patient promptly became symptomless and has remained so (four months). The symptoms in this instance were probably due to spasm of the cerebral vessels. Their disappearance might have been coincidental, but relief was so immediate and lasting that we have attributed it to the effect of the extract.

CONCLUSIONS

The efficacy of a therapeutic measure in a disease such as angina pectoris, with its variability of symptomatology and scarcity of objective findings, should be judged with extreme caution. We have attempted to present our material without prejudice, and urge the reader to draw his own conclusions.

It is our belief that in this series of patients the benefits from this method of treatment have exceeded those obtained by the usual methods. The results were particularly gratifying in intermittent claudication, a disease notoriously refractory to therapeutic endeavor. We do not know the duration of benefit, nor are we certain that the proper dosage and injection intervals have been used to insure maximum effects. Our

number of observations has been comparatively limited. Since, however, a definite trend is evident even in this small group of observations, and since the treatment is without harmful effects and is both simply and expediently given, a wider use of the method is warranted to establish its ultimate worth.

SUMMARY

An insulin-free extract of the pancreas, a vasodilator that modifies the pressor effects of epinephrine and dilates the coronary arteries of the rabbit's heart to a degree exceeding that produced by drugs of the purine group, was administered intramuscularly to twenty patients with angina pectoris. Two, or 10 per cent, were not helped, five, or 25 per cent, were somewhat relieved, eleven, or 55 per cent, were greatly helped, and two who were benefited by treatment died later.

Forty-one patients with angina pectoris who received the usual medical treatment and were followed for a like period of time were studied as a control series. In ten instances, or 24.3 per cent, no benefit was observed, fourteen patients, or 34.1 per cent, experienced moderate relief, fourteen, or 34.1 per cent, received pronounced benefit, and three, or 7.4 per cent, died.

Five patients with intermittent claudication, one with thromboangitis obliterans and one with cerebral vascular spasms and angina pectoris were benefited in a pronounced degree by treatment with the extract.

SOME FACTORS DETERMINING THE INSENSIBLE PERSPIRATION OF MAN

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The insensible perspiration has long been a matter of scientific curiosity, for as far back as 1614 it was the subject of investigation by Sanctorius¹ in what were probably among the first quantitative measurements of human metabolism. The number of papers that have dealt with insensible perspiration within the last few years indicates a revival of interest in it, a renewed endeavor to interpret its physiologic significance and an attempt to explore the possibilities of its clinical application. Experiments have shown that most of the loss in weight (85 per cent) of the human body by insensible perspiration is due to the evaporation of water from the respiratory surfaces and from the skin,² and that within certain limits approximately 25 per cent³ of the total heat lost from the human body is abstracted by the evaporation of water from its surfaces⁴. On these facts has been based the application of measurements of insensible perspiration to the study of energy metabolism.

The unique design of the balance employed by Lombard⁵ made it possible to measure the insensible loss in body weight of a man within a few minutes with great accuracy, although the skill required for its

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1 Sanctorius *Medicina Statica*, translated by John Quincy, ed 2, London, W & J Newton, 1720

2 Benedict, F G, and Benedict, C G *Perspiratio insensibilis. Ihr Wesen und ihre Ursachen*, *Biochem Ztschr* **186** 278, 1927

3 Obviously if visible or sensible (as opposed to insensible) perspiration enters as a factor, the proportion of heat lost from the body by evaporation of water will be increased

4 Benedict, F G, and Carpenter, T M *The Metabolism and Energy Transformations of Healthy Men During Rest*, publ 126, Carnegie Inst Washington, 1910, pp 197 and 241. Soderstrom, G F, and Du Bois, E F *The Water Elimination Through Skin and Respiratory Passages in Health and Disease*, *Arch Int Med* **19** 931 (May) 1917

5 Lombard, W P *A Method of Recording Changes in Body Weight Which Occur Within Short Intervals of Time*, *J A M A* **47** 1790 (Dec 1) 1906

use was such as to render it unsuitable for general requirements. In the meantime a balance capable of weighing 100 Kg with a sensitivity of 0.1 Gm was placed on the market by Sauter of Ebingen, Wurtemberg, Germany. With this type of balance short period determinations of the insensible perspiration were first made with human beings by the Nutrition Laboratory in 1910.⁶ Subsequently, the Sauter balance was used to study the relations between the basal metabolism and the insensible perspiration in a number of normal and pathologic subjects,⁷ and shortly thereafter simultaneous measurements were made of the insensible perspiration and the respiratory metabolism with the special object of noting the proportions of the insensible perspiration derived from the skin and the lungs, respectively.² These measurements indicated that the basal metabolism is proportional to the insensible perspiration. Indeed, a straight line curve has been published⁷ to represent the relationship between the insensible perspiration and the metabolism.

The plans and the results of some of the experiments on insensible loss that have been reported recently indicate that some investigators have not fully sensed the precautions necessary for the successful application of insensible perspiration measurements to physiologic and clinical problems. The procedures by which such determinations have been made during the past few years may be divided into two groups. According to one procedure, the insensible loss in weight of the subject is measured with an accuracy of about 10 Gm, but is observed over a long period, usually overnight. This kind of measurement has undoubtedly a considerable range of usefulness, particularly for clinical purposes, and its possibilities have already been demonstrated.⁷ A second procedure is to employ a sensitive balance for measurements of the changes in body weight occurring in several short (fifteen minute), consecutive periods. The present discussion is limited to this latter type of experiment. In those instances in which the basal metabolism cannot be determined directly by the ordinary methods, these short period measurements have a practical utility because of the ease, the rapidity and the absence of interference with the subject with which they can be made. But the sensitivity (1:1,000,000 that is, 100 Kg:0.1 Gm) of the balance used imposes a limitation difficult to overcome. It is impracticable to avoid completely the use of hygroscopic textiles for the clothing and the covering of the subject during the period of measurement. Because of the avidity with which these materials take up water from the atmosphere of average humidity, one cannot assume that these

6 Benedict, F. G., and Carpenter, T. M. *Respiration Calorimeters for Studying the Respiratory Exchange and Energy Transformations of Man*, publ. 123, Carnegie Inst. Washington, 1910, figs. 4 and 9.

7 Benedict, F. G., and Root, H. F. *Insensible Perspiration: Its Relation to Human Physiology and Pathology*, Arch. Int. Med. **38**:1 (July) 1926.

textiles have a constant weight except under conditions of unchanging humidity of the atmosphere in which the weighings are made. The extremes that can occur in variations in weight due to this factor have been well shown by Heller⁸. He found that the apparent weight of a spring mattress stretched on a wooden frame, covered with a tick, and provided with standard hospital bed covering, underwent an extreme variation of 559.9 Gm during the course of a number of weighings extending over a period of approximately one month. Rates of variation of as much as 8.3 Gm per hour were observed. Variations of this magnitude might introduce serious errors even into short period experiments and yield ridiculous results in long period experiments. It is not at all unlikely, as Heller pointed out,⁸ that some of the contradictory results that have appeared in the latest literature may be due to the nature of the subject's clothing and bed-clothes. Not only must measurements of insensible perspiration be made within short periods, but the hygroscopic material included in the weighings should, theoretically at least, be reduced to a minimum, and the conditions of weighing must be such as to avoid variations in the moisture content of the clothing, so far as possible.

Another important consideration, which appears to have been overlooked in at least one investigation, is that the insensible perspiration is, within limits, affected to the same extent as the metabolism by factors that alter the latter. For measurements of the basal insensible perspiration, basal conditions must be observed as rigorously as for determinations of basal metabolism. If the effect of any activity superimposed on the basal state is to be studied, care must be exercised to ensure that no other factors are allowed to operate which also might affect the metabolism. Neglect of this precaution is, no doubt, responsible for the unexpectedly great difference that Heller and Natanson⁹ have recorded between the rates of insensible perspiration in the recumbent and the upright positions. Another unexpected result is that reported by Jores¹⁰. Under conditions of work, fever and certain diseases he found an absolute parallelism between the changes in basal metabolism and the insensible perspiration, but during sleep at night he noted that the insensible perspiration was greater than during rest in the daytime, this despite the well known depressing effect of sleep on the metabolism.⁴ Jores also claimed that sometimes long periods must elapse after

8 Heller, H. Eine Fehlerquelle bei der Bestimmung der Perspiratio insensibilis mit der Sauterwage, *Ztschr f d ges exper Med* **73** 481, 1930.

9 Heller, H., and Natanson, H. Der Einfluss der aufrechten Körperhaltung auf die extrarenale Wasserausscheidung, *Ztschr f d ges exper Med* **65** 733, 1929.

10 Jores, A. Perspiratio insensibilis, *Ztschr f d ges exper Med* **71** 170, 1930.

the assumption of basal conditions before a steady rate of insensible perspiration is established

Since the experimental results just referred to are at variance with the findings by other investigators on insensible perspiration or are such that they might seriously alter the interpretation of measurements of the insensible perspiration, additional information has been sought experimentally by the Nutrition Laboratory on the following questions

1 The period that must elapse after the assumption of basal conditions before the rate of loss in body weight by insensible perspiration becomes steady

2 The effect on this rate of changing from the recumbent to the sitting position

3 The effect of sleep on this rate (*a*) during the daytime and (*b*) at night

4 The effect produced on the rate by hindering the loss of water by evaporation from the surfaces of the hands and feet ¹¹

THE PERIOD NECESSARY UNDER BASAL CONDITIONS TO ESTABLISH A STEADY RATE OF INSENSIBLE PERSPIRATION

The total duration of the measurements reported by Jores ¹⁰ was always at least two hours. According to him, the rate of insensible loss in weight was faster at the beginning of the measurements, even with subjects accustomed to the procedure, and sometimes the rate first became constant only after one and one-half hours. In the experiments to be discussed in the following pages, the subject (a man) arrived at the laboratory in the morning in the postabsorptive state and was allowed to rest quietly for about one-half hour before measurements were taken. He wore his usual street clothing in all experiments. During the observations he lay on a steel mattress suspended from the beam of a 100 Kg Sauter balance. The mattress was covered with a rubberized sheet and provided with two rubber air pillows. If the statement of the subject or the temperature of the room indicated that the subject was not likely to be comfortably warm during the experiment, he was allowed to lie on a blanket and was covered with another. The subject was weighed by almost counterpoising him by weights (pig-lead or shot) totaling slightly less than his own weight. The beam of the balance was then caused to swing and the time noted at which the swings to each side of the midpoint of the scale were equal. A weight of 10 Gm

¹¹ An interesting point has been reemphasized by the experiments of Kuno and Ikeuchi (*J Orient Med* 7 106, 1927, *ibid* 8 40, 1928) who found that the rate of insensible perspiration from the palms of the hands and the soles of the feet is many times more rapid than that from equal areas of other parts of the body surface

was then placed on the subject's side of the balance and the time noted when the swings again occurred to equal distances from the midpoint. Since the period of swing of the balance was twenty seconds, the time for the instant of equality of the weight of the counterpoise and that of the subject was recorded only to the nearest half minute, that is, with a possible error of \pm fifteen seconds.

In table 1 the rates of insensible perspiration, expressed in grams per hour, are shown for thirteen different experiments. The rates in each experiment have been calculated from the successive periods required for the loss of the first, second and third 10 Gm of body weight. The total duration of each group of observations was approximately one hour. There is a tendency for the rate of insensible perspiration observed

TABLE 1—*Rates of Insensible Perspiration During Successive Periods Required to Lose the First, Second and Third 10 Grams of Body Weight (Subject Lyng, Postabsorptive)*

Experiment	Insensible Perspiration, Gm per Hour		
	Period I	Period II	Period III
1	30.8	26.3	20.2
2	31.6	26.1	29.2
3	29.2	26.6	27.0
4	32.0	28.5	27.9
5	30.8	30.0	26.6
6	36.3	32.8	33.3
7	31.6	26.1	25.0
8	25.0	24.0	26.1
9	26.1	29.2	30.0
10	30.8	30.8	33.3
11*	32.4	27.9	27.2
12*	50.0	46.1	41.4
13*	37.5	33.3	30.0
Average†	30.4	28.0	28.8

* Raining when subject came to laboratory.

† Not including experiments 11, 12 and 13.

during the period of the loss of the first 10 Gm, that is, during approximately the first twenty minutes of the experiment,¹² to be slightly higher than during the periods of loss of the second and third 10 Gm of body weight. There is no such constant difference between the rates during the second and third periods, for in seven of the thirteen experiments the loss during the third period is greater than that during the second period.

On the occasion of experiments 11, 12 and 13 the subject had been exposed to rain on his way to the laboratory. Subsequent examination showed that the ends of his trousers had become damp. The continued

12 Since a certain amount of time was required after the subject lay down to counterpoise him on the balance, the period of measurement of the first 10 Gm of insensible loss corresponded more nearly to thirty or forty minutes after the lying position was assumed, i.e., the time commonly considered prerequisite for the establishment of basal conditions in basal metabolism measurements.

fall in the rate of insensible perspiration in experiments 12 and 13 (not shown in experiment 11) is therefore probably due to the vaporization of water from the damp clothing. It is well known that woolen clothing can take up considerable amounts of water without becoming obviously wet. Any possibility of the action of this factor should be excluded when determinations are to be made of the insensible perspiration. A desirable modification of the routine of such experiments would be to have subjects who come to the laboratory from outside change at least their outer clothing for clothing that has been kept in the laboratory long enough to have reached equilibrium with the existing conditions of humidity.

The average rates of insensible perspiration for the first ten experiments reported in table 1, that is, not including experiments 11, 12 and 13 that were made on rainy days, are 30.4, 28 and 28.8 Gm per hour in the first, second and third periods, respectively. Since there is so little difference between the average rate in the first period and the average rates in the second and third periods, one can consider that the rate of loss is constant almost from the start of the experiment. Certainly these averages and the individual values give no evidence of a continued significant fall in the rate of insensible perspiration after the subject has been lying for thirty minutes (including about fifteen minutes for the adjusting and the counterpoising of the subject on the balance, when the insensible loss is not measured). The conclusion is therefore justified that after the assumption of basal conditions the rate of insensible perspiration becomes constant, for all practical purposes, within thirty minutes. This conclusion is in full conformity with all previous findings by the Nutrition Laboratory, which have demonstrated that under basal conditions when the insensible loss in body weight is plotted with reference to the time, a straight line relationship is invariably noted.

The relative humidity in these experiments varied from 21 to 62 per cent, but, as has been noted in earlier observation in this laboratory, there appeared to be no consistent influence of humidity on the rate of insensible loss.

In two experiments measurements of the basal metabolism were made with the student respiration apparatus¹³ concurrently with the determinations of the insensible perspiration. In one experiment the insensible perspiration in three consecutive periods was 30, 27.7 and 28.2 Gm or, on the average, 28.6 Gm per hour. According to the table published by Benedict and Root⁷ showing the twenty-four hour heat

¹³ Benedict, F. G., and Benedict, C. G. A Student Form of Respiration Apparatus, Boston M. & S. J. **188** 567, 1923, Ein einfacher Respirationsapparat, Skandinav. Arch. f. Physiol. **44** 87, 1923.

production of man predicted from the insensible perspiration per hour, the predicted metabolism when the insensible loss amounts to 28.6 Gm would be 1,381 calories. Three actual metabolism measurements made simultaneously with the observations on insensible perspiration showed values of 1,480, 1,431 and 1,452 calories per twenty-four hours, that is, about 7 per cent higher than the predicted metabolism. In the second experiment the insensible perspiration in five consecutive periods was 30, 32.5, 32, 32 and 35.5 Gm, respectively, averaging 32.4 Gm per hour. The heat production predicted from this average loss would be 1,494 calories per twenty-four hours. Actual measurements of the metabolism gave values of 1,549 calories in each of the first four periods and 1,570 calories in the fifth period, values again but about 7 per cent above the metabolism predicted from the insensible perspiration.

EFFECT OF BODY POSITION ON INSENSIBLE PERSPIRATION

A change in body position is accompanied by a change in metabolism, a somewhat higher metabolism being found in a quiet person when sitting than when lying and a still higher metabolism when standing. The effect of changes in position on the insensible perspiration has been recently studied by Heller and Natanson.⁹ The losses of weight during periods of four hours each were observed by means of a balance having a sensitivity of 10 Gm. Owing to the long periods of measurement it was not practicable to maintain the conditions of bodily rest that are required for determinations of basal metabolism. All the subjects were in the fasting state, but some of them received up to 1,000 cc of water or of a salt solution during the course of the experiment. Those who were in bed were allowed to make slight movements and to converse, but not continually. Those who were in the upright position were allowed to walk quietly about the hospital ward in which the experiments were made, or to sit down, but were not permitted to move about actively, to run, or to assist in carrying things. The result of these vaguely regulated conditions of activity was that the group in bed showed an insensible perspiration from 31 to 46 per cent above the figures predicted¹⁴ from the table of Benedict and Root,⁷ and the upright group showed an increase of from 66 to 83 per cent above those figures. The average figure for the subjects in the upright position exceeded that for the subjects in bed by 36 per cent. Thus seemingly a great influence of change in body position was noted by Heller and Natanson. But the unknown effect of the muscular activity in their experiments renders them wholly unsuitable for showing the influence of

¹⁴ Indirectly derived, after computation of the basal metabolism from the Harris-Benedict prediction tables.

the alteration of position alone on the rate of loss of weight by insensible perspiration

With our subject, some direct, short period measurements were made on the effect of change in position from lying to sitting. The rate of insensible perspiration of the subject while lying was first determined in several short successive periods. The subject was then allowed to rise from the bed in which he had been weighed and to sit quietly in a chair, while the bed was replaced by a chair suspended from the beam of the balance. The subject then moved to the suspended chair, was counterpoised, and the measurements of the rate of insensible perspiration were continued. During the intervals between the actual weighings the feet of the subject were supported, and he was in general made as comfortable and relaxed as possible. After a steady rate of insensible perspiration in the sitting position had been established, the subject left the suspended chair and sat quietly, while the chair was replaced by the

TABLE 2—*Effect of Body Position on Insensible Perspiration (Average Values)*

Experiment	Insensible Perspiration, Gm per Hour		
	Lying	Sitting	Lying
1	29.2	35.5	26.4
2	31.1	32.7	30.5
3	37.5	37.2	25.9
4	29.0	35.9	26.1
Average	31.7	35.3	27.2

bed. He then lay on the bed, and his rate of insensible perspiration was again determined during several short periods in the recumbent position. All the changes of position were made by the subject deliberately and with as little unnecessary exertion as possible. After each change in position sufficient time was allowed to elapse before observing the insensible loss, so that the effect of the muscular effort involved in the actual change in position would not be included in the measurement.

The results of four different experiments to study the effect of body position are recorded in table 2. Each value represents the average of several continuous observations. Change from the lying to the sitting position caused an increase in the insensible perspiration. The individual results varied greatly, however, in spite of the precautions taken. In the third experiment a slight decrease was observed. In this instance the insensible loss in the lying position was exceptionally high, although it remained constant during the period of measurement. Change from the sitting back to the lying position caused a decrease. The individual decreases again showed considerable variation. The insensible perspiration in the four sitting periods is on the average 5.8 Gm. or 20 per cent higher than the average insensible loss in the eight lying periods. This

increase is remarkably large when compared with the average increase of only 4 per cent which Benedict and Benedict¹⁵ found in the metabolism of a person as a result of a change in position from lying to sitting. Their results likewise showed considerable variation, although the greatest increase observed in the metabolism due to sitting was but 10.8 per cent. It was evident that in the measurements reported in table 2 the subject was not made as comfortable as he could have been when sitting in the chair not suspended from the balance. The somewhat constrained position which could not be completely avoided during the periods of actual weighing may likewise have had a greater effect on the metabolism than was anticipated.

INSENSIBLE PERSPIRATION DURING SLEEP

Three experiments were made on the effect of sleep on the insensible perspiration when the sleep occurred during the daytime and one experi-

TABLE 3—*Effect of Sleep in the Daytime on the Insensible Perspiration*

Experiment	Awake		Asleep	
	Total Time, Min	Insensible Loss per Hour, Gm	Total Time, Min	Insensible Loss per Hour, Gm
1	33	27.3	43	27.3
2	27	32.8	27	32.8
3	40	30.5	32	28.6
Average		30.2		29.6

ment when the sleep occurred at night. In the three experiments during the daytime the periods of sleep considered ranged from twenty-seven to forty-three minutes. The insensible perspiration during these periods is compared in table 3 with the corresponding values for periods of wakefulness immediately before or after the periods of sleep. There was no discontinuity of observations during the period of transition from sleep to wakefulness or vice versa. The average insensible perspiration during the periods of wakefulness and sleep was 30.2 and 29.6 Gm per hour, respectively. No significance can be attached to such a small difference between the two values, and the conclusion is that sleep for short periods during the daytime has no appreciable effect on the rate of insensible perspiration.

In the night experiment, recorded in table 4, sixty-three consecutive minutes of wakefulness were followed by seventy-four consecutive minutes of sleep. The length of each separate period was determined

¹⁵ Benedict, F. G., and Benedict, C. G. Influence sur le métabolisme de la position du corps et des moindres mouvements musculaires, *Bull. Soc. scient. d'hyg. aliment.* 12:480, 1924; Body Posture and Minor Muscular Movements as Affecting Heat Production, *Proc. Nat. Acad. Sc.* 10:498, 1924.

by the time required for the loss of 10 Gm in body weight. The observations in this experiment were, unfortunately, not made on the subject in the basal state but were begun about an hour and a half after the ingestion of a light supper consisting of two rolls and butter and a cup of weak tea containing a little milk and sugar. The rate of insensible perspiration changed sharply to a lower level when the subject fell asleep. That this effect is not to be attributed to a gradual fall in insensible perspiration due to the passing off of an initial effect of the food ingested is demonstrated by the values given for the individual periods of the experiment in table 4. These values show clearly that the rate of insensible perspiration varied so slightly during the awake periods that it may be regarded as having been essentially constant. The same is true of the sleep periods. The average insensible perspiration during the awake periods is 28.6 Gm and that during the sleep

TABLE 4—*Effect of Sleep at Night on the Insensible Perspiration*

Condition and Time	Length of Period, Min	Insensible Loss per Hour, Gm
Awake		
7 41 p m		
8 02 p m	21 0	28 6
8 24 p m	21 5	27 9
8 44 p m	20 5	29 3
Average		28 6
Asleep		
9 09 p m	25 0	24 0
9 35 p m	25 5	23 5
9 58 p m	23 5	25 5
10 23 p m	25 0	24 0
Average		24 3

periods is 24.3 Gm per hour. The sleep at night therefore caused an average fall in the rate of insensible perspiration amounting to 15 per cent of the average value for the periods when the subject was awake.

The difference between the effects of sleep in the daytime and at night on the rate of insensible perspiration cannot be ascribed to the difference between the lengths of the periods of sleep under the two conditions. The material change in the rate of insensible perspiration during sleep at night showed itself immediately when the subject fell asleep. The periods of sleep observed in the daytime were long enough to show any similar effect, had it been present. The depth of sleep was not determined in either condition. These results differ fundamentally from those recorded by Jores¹⁰. He found a large increase in the rate of insensible perspiration during sleep at night. This increase was greatest during the earlier portion of the sleep period. The present results are in harmony with the parallel variation that has been shown to hold between metabolism and insensible perspiration, and with the fact that sleep lowers the basal metabolism about 10 per cent.⁴

INSENSIBLE PERSPIRATION FROM HANDS AND FEET

Experiments were made to determine the effect of hindering the insensible loss of water from the hands and feet. In one series of observations the insensible loss from the hands and feet was hindered without otherwise modifying the procedure that has already been described for the determination of the insensible perspiration. In another series the loss from hands and feet was not only obstructed but the feet were warmed at the same time, and in still a third series the loss was hindered from the hands only. The loss of water from the feet was hindered, it not prevented, by covering the feet with rubber overshoes chosen to fit the subject's feet as closely as possible. The upper border of the overshoes was fastened to the skin by a strip of adhesive plaster. The hands were covered with rubber gloves and tightly fitting rubber bands were placed around the wrists over the gloves. The measurements secured when both the hands and feet were covered in this way are given in table 5. In three of the experiments

TABLE 5—*Effect on Insensible Perspiration of Covering the Hands and Feet to Hinder Their Loss of Water*

Experiment	Insensible Perspiration, Gm. per Hour			
	Uncovered	Covered	Uncovered	Covered
1	28.5	20.6	26.2	
2		28.1	33.6	28.6
3	31.6	25.5	31.0	
4	25.3	20.3	24.3	
5		20.4	25.7	

the insensible perspiration was determined in the ordinary way before the hands and feet were covered. In the other two experiments the hands and feet were covered first. The relative humidity varied from 35 to 56 per cent and the room temperature from 16.1 to 25.9 C. In every experiment the rate of insensible perspiration was markedly diminished by hindering the loss from the hands and feet. When the covering was removed after a period long enough to allow equilibrium in the loss to become established again under the altered conditions, the rate of insensible perspiration soon returned to approximately its original value. In these experiments the mean value of the insensible perspiration for all instances when the hands and feet were uncovered was 28.3 Gm. per hour. When they were covered, the average rate fell to 24 Gm. The difference is 4.3 Gm. The insensible loss from the hands and feet therefore amounts, on the average, to 15 per cent of the total insensible perspiration under basal conditions.

It has been shown by Benedict and Benedict² that under basal conditions the loss of water from the skin is approximately 50 per cent of the total insensible perspiration. Since the total insensible loss of

our subject in the experiments reported in table 5 averaged 28.3 Gm per hour, the calculated total loss from the skin would be about 14.2 Gm. By hindering the loss of water from the hands and feet the loss from the skin was decreased by 4.3 Gm. Hence the loss from hands and feet represents 30 per cent of the total skin loss. Du Bois and Du Bois¹⁶ showed that the area of the hands and feet, measured to the wrists and ankles, respectively, amounts to approximately 12 per cent of the total area of the body. The hands and feet must therefore lose water under the conditions of temperature and humidity in our experiments nearly three times as fast per unit of skin area as the rest of the surface of the body per equal unit of skin area.

In two experiments the feet of the subject were heated by applying to the bare soles a rubber water bottle containing water at a temperature as hot as he could endure. Observations under these conditions were made with and without the rubber coverings on the hands and feet. The relative humidity was 55 per cent and the room temperature 20 C. In the first experiment the insensible loss when the extremities were uncovered averaged 4.2 Gm, when they were covered 3.2 Gm, and when they were again uncovered 4.82 Gm per hour. In the second experiment observations made in the same order gave results of 3.91, 2.59 and 3.09 Gm, respectively. According to the data in table 1 the average insensible perspiration of this subject under ordinary basal conditions was about 2.84 Gm per hour. Warming the feet (but with the extremities not covered) caused an increase on the average to 4.05 Gm, that is, an increase of 40 per cent. When the hands and feet were covered, there was, as in the previous experiments reported in table 5, a marked decrease in the rate of insensible perspiration from an average of 4.05 Gm to an average of 2.9 Gm. In these two experiments, therefore, the average decrease amounted to 1.2 Gm, in striking contrast to the decrease of 4.3 Gm noted in the experiments recorded in table 5 in which the feet had not previously been warmed.

In two experiments the effect on the insensible perspiration of covering the hands alone was observed. A diminution of the insensible loss was noted, although to a lesser degree than when both hands and feet were covered.

The experiments reported in the foregoing pages accentuate the importance of observing strictly basal conditions when one is measuring insensible perspiration. The experience of the Nutrition Laboratory, certain hospital usage in Boston, and particularly the experience of Professor Newburgh,¹⁷ emphasize the belief that the accurate measure-

16 Du Bois, D., and Du Bois, E. F. The Measurement of the Surface Area of Man, *Arch Int Med* **15** 868 (May) 1915.

17 Newburgh, L. H., and Johnston, M. W. The Exchange of Energy Between Man and the Environment, Springfield, Ill., Charles C. Thomas, 1930.

ment of the insensible perspiration may have considerable clinical value. The method has its limitations, which must be clearly recognized, and it is obvious that it must not be misused.

SUMMARY

1 When measured under the usual conditions obtaining in basal metabolism experiments, the rate of insensible perspiration of an adult man became constant within thirty minutes after the assumption of the lying position.

2 Changing from the lying to the sitting position caused an increase of 20 per cent in the rate of insensible perspiration under the special experimental conditions.

3 Sleep during the daytime had no significant effect on the rate of insensible perspiration. Sleep at night lowered it markedly.

4 About 15 per cent of the total loss by insensible perspiration was due to the loss from the surfaces of the hands and feet. Of the total skin loss, 30 per cent was derived from the surfaces of the hands and feet.

5 The rate of loss from the hands and feet was approximately three times greater than that from the rest of the skin per equal unit of skin area.

6 Heating the feet increased the loss by insensible perspiration considerably.

CLINICAL SIGNIFICANCE OF VOLUME AND HEMOGLOBIN CONTENT OF THE RED BLOOD CELL

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CLEVELAND

In 1864, Welcher¹ described the first method for determining the volume of the erythrocyte and measured in cubic microns the volume of the normal cell of man and of many lower animals. By his ingenious, but inaccurate, method, Welcher also showed that in chlorosis the red cells may be smaller than normal and thus he made the first clinical application of the determination of the volume of the erythrocyte. Hayem,² the father of clinical hematology, early recognized the importance of variation in the size of the red cells although he measured only the diameter. Laache,³ in the first monograph on anemia, measured the diameter of the red cells in every case of anemia, and showed especially the great significance of macrocytosis of the erythrocytes in pernicious anemia. Malassez,⁴ one of the important early contributors to hematology, reported the hemoglobin content in micromicrograms per cell in different types of anemia. Using Welcher's figures for the volume of the normal cell, Malassez calculated the hemoglobin also in percentage per unit volume of cell. Similar calculations were made by Hart⁵ in 1881.

Hedin's development of the hematocrit⁶ afforded the first simple and direct method for determining the volume of the red blood cell. Herz⁷ first used the hematocrit to measure the mean individual cell volume, which he designated "das mittlere Volumen der einzelnen Zellen." He calculated also the "specific hemoglobin content of the cell," which is the same as the saturation index. It remained, however, for Capps⁸ to demonstrate, in 1903, the clinical significance of varia-

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1 Welcher, H. Grosse, Zahl, Volum, Oberflache und Farbe der Blutkörperchen bei Menschen und bei Tieren, *Ztschr. f. rat. Med.* **20** 257, 1863.

2 Hayem, G. Recherches sur l'anatomie normale et pathologique du sang, Paris, Masson & Cie, 1878, p. 143.

3 Laache, S. Die Anämie, Kristiania, Mallings, 1883, p. 276.

4 Malassez, L. Sur la richesse en hémoglobine des globules rouges du sang, *Arch. de physiol. norm. et path.* **4** 637, 1877.

5 Hart, E. Micrometric Numeration of the Blood Corpuscles and the Estimation of Their Hemoglobin, *Quart. J. Micr. Sc.* **21** 132, 1881.

6 Hedin, S. G. Hamatokriten, en ny apparat för blodundersökning, Skandinav. *Arch. f. Physiol.* **2** 134, 1890-1891.

7 Herz, M. Blutkrankheiten, *Virchows Arch. f. path. Anat.* **133** 339, 1893.

8 Capps, J. A. A Study of Volume Index. Observations upon the Volume of the Erythrocyte in Various Diseased Conditions, *J. M. Research* **10** 367, 1903.

tions in the volume of the average erythrocyte, which he recorded in terms of his volume index. Following Capps' important contribution little use was made of cell volume determinations by hematologists for a number of years. In the past ten years, however, interest in this phase of blood studies has been revived, and a number of articles on cell size have appeared.⁹

It is the purpose of this paper to summarize the clinical significance of the accurate determination of the volume and hemoglobin content of the red cell in health and disease and to report the results of such studies on 444 normal and abnormal persons.

METHODS

In determining the relative red cell volume, I have used the hematocrit method. This method has been criticized, especially by Ponder and Saslow,¹⁰ as not giving

9. Alder, Albert. Viscosimetrisches Blutkörperchenvolumbestimmung. Studien über Grösse und Hämoglobinfüllung der Erythrocyte. *Cor-Bla* 1 Schweiz. Aerzte 48 1405, 1918. Bomlinger, M. Die Bedeutung des Blutkörperchenvolumens für die klinische Blutuntersuchung, *Ztschr f klin Med* 87 450, 1919. Csaki, L. Die Volummessung der rothen Blutkörperchen bei verschiedenen Krankheiten, *Ztschr f klin Med* 93 405, 1922. Froelich, Carrie. Ueber genaue Bestimmung des Farbeindex der roten Blutkörperchen, Farbeindex (Zahl) und Farbeindex (Volumen), *Folia haemat* 27 109, 1921-1922. Hayden, R. L. Accurate Criteria for Differentiating Anemias, *Arch Int Med* 31 766 (May) 1923. Rossdale, George. Observations with the Hematocrit Volume-Colour Index, *Quart J Med* 16 245, 1923. Hayden, R. L. The Value of Volume Index in the Diagnosis of Pernicious Anemia, *J. A. M. A* 83 671 (Aug 30) 1924. The Volume and Hemoglobin Content of the Erythrocyte in Health and Disease, *Folia haemat* 31 113, 1925. von Boros, J. Ueber Grösse, Volumen und Form der menschlichen Erythrozyten und deren Zusammenhang. *Wien Arch f inn Med* 12 243, 1926. Osgood, E. C. Hemoglobin, Color Index, Saturation Index and Volume Index Standards, *Arch Int Med* 37 685 (May) 1926. Osgood, E. C., and Haskins, H. D. Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, *Arch Int Med* 39 634 (May) 1927. Jorgensen, S., and Warburg, E. J. The Indices and Diameters of the Erythrocytes and the Best Hematological Criterion of Pernicious Anemia, *Acta med Scandinav* 46 109, 1927. Wintrobe, M. M., and Miller, M. W. Normal Blood Determinations in the South, *Arch Int Med* 43 96 (Jan) 1929. Wintrobe, M. M. Blood of Normal Young Women Residing in a Subtropical Climate, *Arch Int Med* 45 287 (Feb) 1930. The Volume and Hemoglobin Content of the Red Blood Corpuscle, *Am J M Sc* 177 513, 1929. Murphy, W. P., and Fitzhugh, G. Red Blood Cell Size in Anemia. Its Value in Differential Diagnosis, *Arch Int Med* 46 440 (Sept) 1930. Wintrobe, M. M. Hemoglobin Content, Volume, and Thickness of the Red Blood Corpuscle in Pernicious Anemia and Sprue, and the Changes Associated with Liver Therapy, *Am J M Sc* 181 217, 1931. Hayden, R. L. Methods and Clinical Value of the Determination of the Size of the Red Blood Cell, *Am J M Sc* 181 597, 1931.

10. Ponder, E., and Saslow, G. The Measurement of Red Cell Volume, *J Physiol* 70 18, 1930.

correct absolute values. It remains, however, the one practical method available, and when properly done gives values that check closely with those of other entirely different methods, such as that devised by Bleibtreu¹¹

In the hematocrit method an anticoagulant that does not change the volume of the cells should be employed. Hirudin and heparin are satisfactory but expensive. I have used an isotonic (14 per cent) solution of sodium oxalate,¹² which is decidedly preferable to a solid or a concentrated solution of sodium or potassium oxalate which shrinks the cells. The only advantage of the latter procedure is the use of smaller amounts of blood, yet there is seldom any objection to taking 20 cc of blood from a patient. The greater the extent of the anemia the smaller the volume of cells removed, so the amount of cells removed is always relatively the same. A normal person has roughly 2,500 cc of packed cells, hence, in taking 20 cc of blood, about one two hundred and fiftieth or 0.4 per cent of the total cell volume is removed. Since the blood volume changes little, a person with a cell volume of 40 per cent of normal would have only 4 cc of packed cells removed, which is still 0.25 per cent of the amount of cells present.

My procedure is as follows. I remove 20 cc of blood from the median basilic vein, and add exactly 10 cc to 2 cc of 14 per cent sodium oxalate solution contained in an accurately graduated 12 or 15 cc centrifuge tube. This is spun in an International no. 2 centrifuge for one hour at 2,500 revolutions per minute. The remaining 10 cc has 2 drops of a saturated solution of potassium oxalate added to it and is used for the cell count and hemoglobin determination. All cell counts have been made with counting chambers and pipets certified as correct by the United States Bureau of Standards. Nearly all the hemoglobin estimations have been done by the oxygen capacity method using the Van Slyke apparatus. Recently hemoglobin readings have been made with the Haden-Hausser hemoglobinometer¹³ which has given readings that check closely with the gasometric procedure. The determinations that were made by means of the hemoglobinometer are indicated in the tables by a star. The number of determinations made by this method is only 31 among a total of over 500 determinations reported here.

In calculating the percentage of hemoglobin, 154 Gm per hundred cubic centimeters is taken as 100 per cent since this is the average amount that I have found per hundred cubic centimeters per five million cells in 100 normal men and women. The amount of packed cells will vary somewhat, although very little, with the time and force of centrifugation. With one centrifugation for one-half hour, 48 cc of packed cells per hundred cubic centimeters per five million cells was obtained, with another for one hour, 45 cc. With the centrifuge used most of the time and employing one hour's centrifugation 46 cc was obtained, so all the results have been corrected to this figure, which is taken as 100 per cent.

The size of the cell may be measured by determining the diameter. Since the volume varies as the cube of the diameter, it is apparent that the volume is a much more sensitive indicator of variation in size than is the diameter. This point is illustrated in figure 1.

11 Bleibtreu, M, and Bleibtreu, L. Eine Methode zur Bestimmung des Volums der körperliche Elemente in Blut, *Arch f d ges Physiol* **51** 151, 1891-1892

12 Haden, R. L. The Technique of Determination of the Relative Mass, the Individual Cell Volume and the Volume Index of the Erythrocytes of Man, *J Lab & Clin Med* **15** 736, 1930

13 Haden, R. L. A New Hemoglobinometer, *J Lab & Clin Med* **16** 68, 1930

TERMINOLOGY

Number—The number index is the number of erythrocytes relative to normal (5,000,000 equals 100 per cent)

Volume—The volume coefficient¹⁴ is the number of cubic centimeters of packed cells per five million cells per hundred cubic centimeters of blood. This is calculated by dividing the number of cubic centimeters of packed cells per hundred cubic centimeters by the number index. The normal volume coefficient in this series was 46

The mean corpuscular volume¹⁵ is the mean volume of a single red blood cell in cubic microns. This is calculated by dividing the volume of packed cells in a unit volume of blood by the number of cells contained therein. The normal in this series was 92 cubic microns

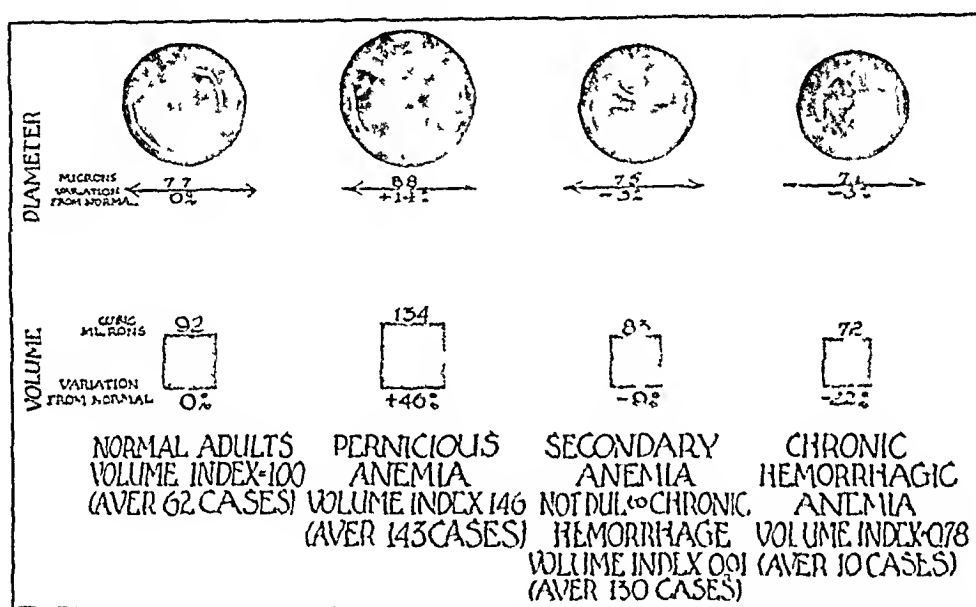


Fig 1—Relation of cell volume to cell diameter. The mean corpuscular volume is the most sensitive indicator of variation in cell size

The volume index is the mean volume of a single red cell relative to normal. This is calculated by dividing the volume of packed cells in per cent of normal by the number of cells in per cent of normal, or the number index, or by dividing the observed mean corpuscular volume by the normal mean corpuscular volume. The normal limits of the volume index are taken as 0.90 and 1.10

Hemoglobin Content—The hemoglobin coefficient¹⁴ is the number of grams of hemoglobin per five million cells per hundred cubic centimeters of blood. This is calculated by dividing the observed number of grams of hemoglobin per hundred cubic centimeters by the number index. The normal hemoglobin coefficient in this series was 15.4 Gm

¹⁴ Term suggested by Osgood

¹⁵ Term suggested by Wintrobe

The mean corpuscular hemoglobin ¹⁵ is the mean hemoglobin content of a single red cell in micromicrograms. This is calculated by dividing the number of micrograms of hemoglobin in a unit volume of blood by the number of cells contained therein. The normal mean corpuscular hemoglobin content in my series was 30.8 micromicrograms.

The color index is the mean hemoglobin content of a single cell relative to normal. This is calculated by dividing the hemoglobin in per cent of normal by the number of cells in per cent of normal or the number index, or by dividing the observed mean corpuscular hemoglobin by the normal mean corpuscular hemoglobin. The normal limits of the color index are taken as 0.90 and 1.10.

Hemoglobin Concentration—The mean corpuscular hemoglobin concentration ¹⁵ is the mean hemoglobin concentration in per cent per unit volume of cells. This is calculated by dividing the hemoglobin in a unit volume of blood by the volume of packed cells contained therein. The normal corpuscular hemoglobin concentration in this series was 33.7 per cent.

The saturation index is the mean corpuscular hemoglobin concentration relative to normal. This is calculated by dividing the hemoglobin in per cent of normal by the number of packed red cells in per cent of normal, or by dividing the color index by the volume index. The normal limits of the color index are taken as 0.90 and 1.10.

The absolute volumes for the red cell constants seemingly vary geographically ¹⁶. For this reason it seems preferable in clinical work to express the volume, hemoglobin content and hemoglobin concentration in per cent of normal (volume, color and saturation index) rather than in cubic microns, micromicrograms and per cent. With correct adjustment the indexes are everywhere always within normal limits (0.90 and 1.10), even with a great difference in the volume of the average cell in cubic microns and in the hemoglobin content in micromicrograms.

NORMAL OBSERVATIONS

The uniformity of the volume and hemoglobin content of the red cell in healthy persons in a given location is most remarkable. There is little variation in cell size in different persons, and single cells vary only within very narrow limits. In determining my standards, I have studied 100 normal men and women by the methods described. The typical determinations in 10 persons and a summary for the entire group are shown in table 1. The cell volume, hemoglobin content and hemoglobin concentration did not vary from the mean more than ± 10 per cent and in few persons more than ± 5 per cent. The volume

16 Haden, R. L. The Geographic Variation in the Size of the Red Cells, *J Lab & Clin Med* 14:1120, 1929.

TABLE 1—*Determinations in One Hundred Normal Men and Women*

Sex	Packed Red Cells				Mean Corpuscular Volume, Cubic Microns	Hemoglobin			Mean Corpuscular Hemoglobin, Micrograms	Color Index	Mean Hemoglobin Concentration, per Cent	Saturation Index	
	Red Blood Cells per Cc Min.	Hematocrit Reading, per 100 Cc.	Per Cent of Normal	Volume Coefficient, Cc		Volume Index	Gm per 100 Cc	Per Cent of Normal					Hemo globin Coefficient, Gm
Typical Determinations													
M	4.06	44	96	45	0.98	15.86	98	15.4	0.5	1.00	31.2	1.02	
M	4.73	42	91	44	0.96	14.95	97	15.8	31.6	1.03	35.9	1.07	
M	4.52	44	96	48	1.04	15.02	91	15.5	31.0	1.01	32.7	0.97	
M	5.66	47	100	46	1.01	15.12	100	15.2	20.1	0.99	33.1	0.98	
M	5.02	46	100	46	1.00	15.52	101	15.1	20.9	1.00	33.7	1.00	
M	5.18	49	106	47	1.02	16.50	107	15.9	31.8	1.03	23.9	1.01	
F	4.03	38	83	47	1.00	13.15	85	16.1	32.6	1.05	35.7	1.06	
F	4.35	40	87	46	1.00	12.70	88	11.6	29.2	0.95	32.1	0.95	
F	4.62	41	89	45	0.98	12.26	86	11.4	28.8	0.94	32.4	0.96	
F	4.74	43	94	45	0.98	14.35	91	15.2	0.1	0.99	34.0	1.01	
Summary													
	4.78	42.7	95	46	1.00	14.75	95	15.45	20.8	1.00	33.7	1.00	

coefficient was 46, the hemoglobin coefficient 15.4 Gm and the hemoglobin concentration 33.7 per cent. The average volume, color and saturation indexes were 1.00. These figures were taken as 100 per cent in calculating the percentages and indexes. The normal observations in 100 men and women are shown graphically in figure 2.

LABORATORY CLASSIFICATION OF ANEMIA ON THE BASIS OF VOLUME AND HEMOGLOBIN CONTENT

The laboratory classification of anemia has always been unsatisfactory. A rough differentiation into primary and secondary types is frequently used. The anemias showing a color index greater than 1.00

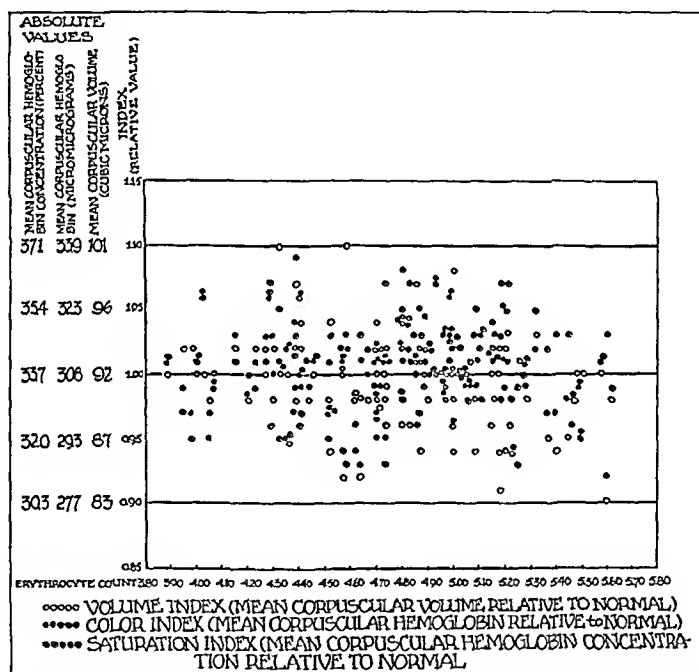


Fig. 2—The indexes and erythrocyte constants in 100 normal men and women. Note the very slight variation for the entire group.

are usually classified as primary and those showing a color index of 1.00 or less as secondary. Hampson and Shackle¹⁷ have suggested the classification of anemias on the basis of cell size, using the terms megalocytic and nonmegalocytic. Wintrobe¹⁸ suggested four groups: (1) macrocytic, (2) normocytic, (3) simple microcytic and (4) hypochromic. Certainly the most logical laboratory classification is based

17 Hampson, A. C., and Shackle, J. W. Megalocytic and Nonmegalocytic Anemia, *Guy's Hosp. Rep.* **74**: 193, 1924.

18 Wintrobe, M. M. Classification of the Anemias on the Basis of Differences in Size and Hemoglobin Content of the Red Corpuscles, *Proc. Soc. Exper. Biol. & Med.* **27**: 1071, 1930.

on all three variables of the erythrocyte, namely, number, size and hemoglobin content. The following terms may well be employed to indicate variations that have been observed in these factors:

Number	<div>Hypercythemie red cell count > normal</div> <div>Normocythemie red cell count within normal limits</div> <div>Hypocythemie red cell count < normal</div>
Volume	<div>Macrocytic mean corpuscular volume > normal (VI > 110)</div> <div>Normocytic mean corpuscular volume, normal (VI = 0.90-1.10)</div> <div>Microcytic mean corpuscular volume < normal (VI < 0.90)</div>
Hemoglobin content	<div>Hyperchromic mean corpuscular hemoglobin > normal (CI > 1.10)</div> <div>Normochromic mean corpuscular hemoglobin, normal (CI = 0.90-1.10)</div> <div>Hypochromic mean corpuscular hemoglobin < normal (CI < 0.90)</div>

All the different types of anemia that may occur from this standpoint are

Normocythemie	<div>Normocytic and hypochromic</div> <div>Microcytic and hypochromic</div>
Hypercythemie	<div>Normocytic and hypochromic</div> <div>Microcytic and hypochromic</div>
Hypocythemie	<div>Macrocytic and hyperchromic</div> <div>Macrocytic and normochromic</div> <div>Macrocytic and hypochromic</div> <div>Normocytic and normochromic</div> <div>Normocytic and hypochromic</div> <div>Microcytic and hypochromic</div>

TYPES OF ANEMIA											
MEAN CORPUSCULAR VOLUME IN PER CENT OF NORMAL											
REL. VES. DIA. & HEMOGLOBIN CONTENT											
INDEXES											
NUMBER INDEX	0.90-1.10	<0.80	<0.80	<0.80	<0.90	<0.90	0.90-1.10	>1.10	0.90-1.10	<0.90	>1.10
VOLUME INDEX	0.90-1.10	>1.10	>1.10	>1.10	0.90-1.10	0.90-1.10	0.90-1.10	0.90-1.10	<0.90	<0.90	<0.90
COLOR INDEX	0.90-1.10	>1.10	0.90-1.10	<0.90	0.90-1.10	<0.90	<0.90	<0.90	<0.90	<0.90	<0.90
SATURATION INDEX	0.90-1.10	0.90-1.10	<0.90	<0.90	0.90-1.10	<0.90	<0.90	<0.90	VARIABLE	VARIABLE	VARIABLE
TYPICAL US. SAMPLE											
CELL COUNT	5 MILLIONS	2.0	3.0	2.50	3.50	3.70	5.00	5.00	5.00	5.00	5.00
VOLUME INDEX	1.00	1.50	1.25	1.20	1.00	0.96	0.95	0.90	0.80	0.10	0.10
COLOR INDEX	1.00	1.40	1.00	0.84	0.95	0.70	0.60	0.60	0.60	0.50	0.50
SATURATION IND.	1.00	0.93	0.80	0.70	0.95	0.73	0.65	0.55	0.75	0.71	0.71
CLASSIFICATION OF BLOOD	HYPERCYTHIC AND HYPERCHROMIC BLOOD	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA	HYPOCYTHIC AND MICROCYTIC ANEMIA

Fig 3—The different types of anemia classified on the basis of number, volume and hemoglobin content of the erythrocytes

These different types of anemia are illustrated in figure 3. The circles indicate relative volume, not diameter, and the intensity of color indicates the relative hemoglobin content. A typical example of each type of anemia is given. Every anemia should be thought of in terms of number, volume and hemoglobin content of the average erythrocyte, and every case should be classified on such criteria. An anemia with a red cell count of 3.50 millions, a volume index of 0.75 and a color index of 0.65 is reported as a hypocythemie, microcytic and hypochromic anemia rather than simply as "secondary" anemia. Likewise

an anemia with a count of 2 00 millions and a volume and color index of 1 50 is recorded as hypocythemic, macrocytic and hyperchromic rather than "primary"

OBSERVATIONS IN DIFFERENT CLINICAL GROUPS OF ANEMIA

The clinical classification of anemia is even more confusing than the laboratory classification. Every anemia, however, is due to increased blood loss or decreased blood formation or to a combination of these two factors. Increased blood loss may be mechanical or may result from increased destruction within the body, and the anemias due to decreased blood formation may result from a qualitative depression of bone marrow activity or may be the result of quantitative defect due to an actual decrease in bone marrow tissue. The clinical classification of anemia that I have used with the more common causes in each group is as follows

I Increased blood loss (acute or chronic)

A Mechanical loss

- 1 Uterine bleeding
- 2 Hemorrhoids
- 3 Peptic ulcer
- 4 Disturbances of blood coagulation
- 5 Trauma

B Accelerated destruction

- 1 Chronic hemolytic jaundice
- 2 Acute hemolytic anemia
- 3 Splenic anemia

II Decreased blood formation

A Qualitative defect

- 1 Malignant growth
- 2 Infection
- 3 Chronic intoxication
- 4 Metabolic disturbance
- 5 Dietary deficiency
- 6 Achlorhydria (simple)
- 7 Pernicious anemia

B Quantitative defect

- 1 A decrease in the bone marrow by bone disease, malignant or leukemic infiltration

I have grouped all the anemias studied according to this clinical classification. In the tables typical examples of the different types are given to show the extremes of the determinations. In table 2 are shown the anemias due to acute mechanical blood loss. Here the number of cells is reduced without change in the mean volume, and with little change in the hemoglobin content. A part of the circulating blood is sliced off, so to speak, and the fraction remaining is relatively normal.

TABLE 2—Determinations in Anemia Due to Mechanical Blood Loss from Acute Hemorrhage

Red Blood Cells per Cu. Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Hemoglobin			Gm per 100 Cc.	Hemo globin, Micrograms			Color Index	Saturation Index	Diagnosis
	Hematocrit Reading, per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc.		Per Cent of Coefficient, Gm	Hemo globin, Micrograms	Color Index		Saturation Index					
0.93	9	20	50	100	2.31	15	12.3	21.6	0.80	0.72	Hemophilia			
1.08	12	25	51	102	2.56	23	16.2	32.4	1.05	0.92	Duodenal ulcer			
1.38	12	27	45	90	3.85	25	14.0	28.0	0.91	0.90	Essential thrombopenia			
1.65	15	33	46	92	4.63	0	13.8	27.6	0.90	0.90	Gastric hemorrhage			
2.00	21	51	50	100	7.55	49	15.1	30.2	0.98	0.91	Hemophilia			
2.62	21	70	45	90	6.78	14	13.1	26.2	0.85	0.88	Gastric hemorrhage			
3.05	29	62	47	94	8.61	76	14.0	28.0	0.91	0.90	Hemophilia			
3.44	32	69	46	92	9.57	64	14	28.6	0.93	0.93	Essential thrombopenia			
3.76	35	75	46	92	11.52	75	15.4	30.8	1.00	1.00	Hemophilia			
4.17	37	80	45	90	11.00	71*	13.1	26.2	0.85	0.89	Gastric hemorrhage			
						Summary								
2.37	22	47	46	92	6.62	13	14.17	28.3	0.92	0.92	Average in 14 cases			

* Determination made by means of the hemoglobinometer

TABLE 3—Determinations in Anemia Due to Mechanical Blood Loss from Chronic Hemorrhage

Red Blood Cells per Cu Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Hemoglobin				Mean Corpuscular Hemoglobin, Micrograms	Color Index	Saturation Index	Diagnosis
	Hematocrit Reading, per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc.		Gm per 100 Cc.	Per Cent of Normal	Hemo-globin Coefficient, Gm					
								Typical Determinations				
1.53	15	42	48	96	3.23	21	10.6	21.2	0.69	0.66	Hemorrhoids	
1.98	15	33	59	78	3.59	22	8.5	16.9	0.55	0.67	Essential thrombopenia	
2.04	19	42	47	94	4.65	30	11.2	22.1	0.73	0.71	Menorrhagia	
2.41	16	35	33	66	4.16	27	8.6	17.3	0.56	0.77	Hemorrhoids	
3.00	22	47	26	79	5.70	37	9.6	19.1	0.62	0.79	Hemorrhoids	
3.07	26	76	41	82	5.70	37	9.2	18.5	0.60	0.67	Hemorrhoids	
3.24	24	72	37	74	6.32	41	9.7	19.1	0.63	0.79	Menorrhagia	
3.43	29	63	42	84	7.85	51	11.1	22.8	0.71	0.81	Menorrhagia	
3.93	31	67	31	68	8.78	57	11.2	22.4	0.73	0.85	Gastric ulcer	
4.17	25	54	30	69	6.93	45*	9.2	16.3	0.55	0.84	Menorrhagia	
Summary												
2.5	25	54	38	76	6.62	47	10.2	20.1	0.66	0.80	Average in 14 cases	

* Determination made by means of the hemoglobinometer

In chronic mechanical blood loss the determinations are quite different (table 3). Here with a varying cell count the mean cell volume is practically always decreased and the hemoglobin content decreased even more. The average cell count in this group was 3.25 millions, the volume index 0.83, the color index 0.66 and the saturation index 0.90.

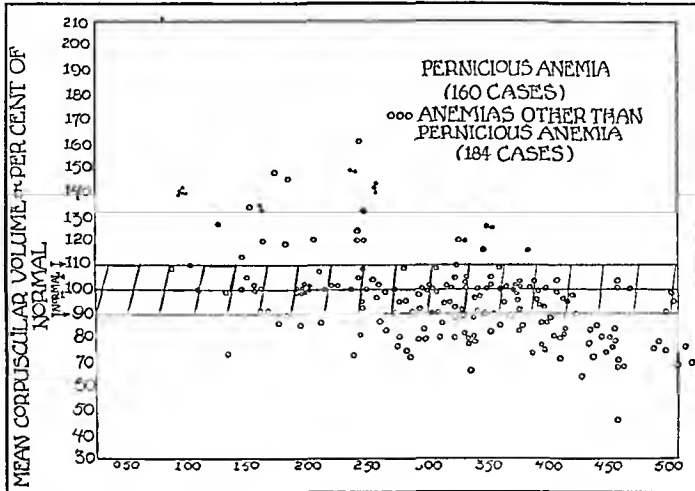


Fig. 4—The mean corpuscular volume of the erythrocyte in pernicious anemia contrasted with that in other types of anemia. The volume is constantly high in pernicious anemia and seldom above normal in other types.

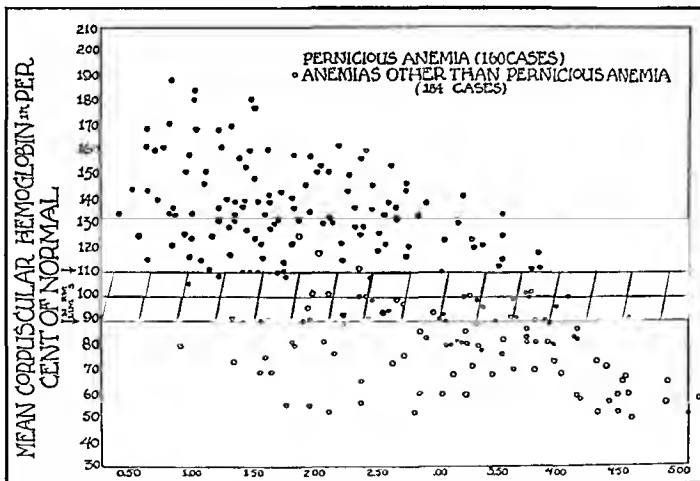


Fig. 5—The mean corpuscular hemoglobin of the erythrocyte in pernicious anemia contrasted with that in other types of anemia.

The anemias due to increased blood destruction constitute an interesting group (table 4). The cell volume is seldom decreased and is often increased. If many reticulocytes are present, the average volume is usually greater than normal since reticulocytes tend to be larger than normal. The average cell count in this group was 2.69, the volume index 1.04, the color index 0.93 and the saturation index 0.93.

TABLE 4—*Determinations in Anemia Due to Increased Blood Loss from Accelerated Blood Destruction*

Red Blood Cells per Cu Mm., Millions	Packed Red Cells			Mean Corpus- cular Volume, Cubic Microns	Hemoglobin				Mean Cor- puscular Hemo- globin, Micro- grams	Color Index	Mean Corpuscular Hemoglobin, Concen- tration, per Cent	Saturation Index	Diagnosis
	Hematocrit Reading, per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc		Gm per 100 Cc.	Per Cent of Normal	Hemo- globin Coefficient, Gm	Hemo- globin Micro- grams					
150	16	34	52	104	5.08	33	16.9	33.9	1.10	32.4	0.97	Acute hemolytic anemia (infection)	
158	19	42	64	123	6.00	34	16.9	33.9	1.10	27.4	0.52	Splenic anemia	
183	24	53	66	132	6.93	45*	19.2	35.5	1.25	27.0	0.81	Chronic hemolytic jaundice	
205	22	48	54	108	7.10	48*	18.0	36.0	1.17	33.7	1.00	Chronic hemolytic jaundice	
234	27	37	56	112	8.02	72*	17.1	31.2	1.11	30.1	0.90	Phenylhydrazine poisoning	
243	27	60	55	110	7.55	49	14.5	29.0	1.00	27.0	0.81	Toxic hepatitis	
250	21	17	43	86	7.24	47	11.5	29.0	0.91	33.5	1.00	Banti's disease	
250	27	60	57	110	8.72	54	15.6	31.3	0.90	0.1	0.60	von Nothmann's anemia	
355	29	64	42	84	8.78	57*	12.3	21.6	0.80	26.7	0.80	Banti's disease	
362	37	81	43	96	11.05	72	13.8	27.7	0.90	29.7	0.89	Chronic hemolytic jaundice	
437	33	71	38	76	9.10	61*	10.6	21.2	0.69	29.0	0.86	Banti's disease	
Summary													
269	26	56	48	96	7.70	70	14.3	23.6	0.93	29.7	0.89	Average in 15 cases	

* Determination made by means of the hemoglobinometer

TABLE 5—Determinations of a Qualitative Defect in Blood Formation

Red Blood Cells per Cu Mm., Millions	Packed Red Cells			Mean Corpus- cular Volume, Cubic Microns	Volume Index	Hemoglobin			Mean Cor- puscular Hemo- globin, Micro- grams	Color Index	Mean Corpuscular Hemoglobin, Concen- tration, per Cent	Saturation Index	Diagnosis
	Hematocrit Reading in Cc per 100 Cc.	Per Cent of Normal	Volume Coeffi- cient, Cc			Gm per 100 Cc	Per Cent Normal	Hemo globin Gm					
Typical Determinations													
160	15	33	47	94	1.03	4.17	27	13.8	27.6	0.90	29.1	0.87	Chronic nephritis
169	14	31	42	84	0.91	3.54	23	10.5	21.0	0.68	25.1	0.75	Cancer of the uterus
197	18	39	45	90	0.99	4.62	30	11.5	23.1	0.75	25.7	0.77	Malnutrition
201	19	42	47	94	1.02	6.47	42	15.7	31.4	1.02	33.5	1.00	Chronic nephritis
201	18	40	45	90	0.98	6.17	29	10.8	21.5	0.70	24.1	0.72	Achlorhydria
210	20	44	48	96	1.05	5.24	34	12.5	25.0	0.81	25.7	0.77	Malnutrition
214	17	37	40	80	0.86	3.54	23	8.2	16.3	0.53	20.8	0.62	Dietary deficiency
221	21	46	47	94	1.02	6.00	39	13.6	27.1	0.88	28.7	0.86	Cancer of the colon
226	21	46	47	94	1.02	7.10	46	15.7	31.4	1.02	33.5	1.00	Focal infection
252	23	50	46	92	1.00	5.70	37	11.4	22.8	0.74	24.8	0.74	Achlorhydria
267	24	52	45	90	0.98	6.78	44	12.6	25.3	0.82	28.4	0.85	Chronic bronchitis
283	25	54	44	88	0.95	6.00	39	10.5	21.0	0.68	24.1	0.72	Cancer of the cervix
285	19	42	34	68	0.74	4.62	30	8.2	16.3	0.53	23.8	0.71	Anemia of pregnancy
310	28	61	46	92	0.99	7.85	51	12.8	25.5	0.83	27.4	0.82	Deficiency disease
314	25	54	40	80	0.86	6.47	42	10.2	20.5	0.67	26.0	0.78	Anemia of pregnancy
321	30	65	47	94	1.01	8.00	52	12.5	25.0	0.81	26.7	0.80	Lead poisoning
327	34	73	51	102	1.10	10.00	65	15.4	30.8	1.00	30.1	0.90	Subpectoral abscess
331	28	61	42	84	0.82	7.70	50	14.2	28.3	0.76	27.7	0.83	Cancer of the stomach
340	32	70	47	94	1.03	10.00	65	14.8	29.6	0.96	31.1	0.98	Myxedema
340	27	59	40	80	0.97	7.51	49	11.1	22.2	0.72	27.7	0.83	Oral sepsis
345	31	67	45	90	0.97	9.25	60	13.4	26.8	0.87	30.1	0.90	Chronic cholecystitis
350	29	63	41	82	0.90	9.70	63	13.9	27.7	0.90	33.5	1.00	Cirrhosis of the liver
350	31	67	44	88	0.95	10.00	65	14.3	28.6	0.93	32.4	0.97	Deficiency disease
364	34	73	46	92	1.00	10.30	67	14.2	28.3	0.92	30.7	0.92	Achlorhydria
371	30	65	41	82	0.88	6.00	39	8.8	17.6	0.57	20.1	0.60	Oedema
411	39	95	48	96	1.04	12.00	82	11.5	29.0	1.00	32.1	0.96	Cancer of the colon
419	34	75	41	82	0.89	7.40	48	8.8	17.6	0.57	21.4	0.64	Achlorhydria
461	47	95	47	94	1.03	12.30	80	13.4	26.8	0.87	28.4	0.85	Chlorosis
526	30	66	29	58	0.63	6.93	45*	6.5	12.9	0.42	22.8	0.68	Achlorhydria
596	37	80	31	62	0.67	9.40	61*	7.9	15.7	0.51	25.4	0.76	Hypothyroidism
Summary in 110 cases													
346	27	59	39	78	0.86	8.2	53	11.9	23.7	0.77	30.1	0.90	

* Determination made by means of the hemoglobinometer

The anemias due to defective blood formation make up by far the largest group (table 5). The pernicious anemia group is summarized separately. In table 5 are shown the typical determinations in 30 cases of anemia other than pernicious anemia due to a depression of bone marrow formation. These anemias vary greatly, in many there is relatively little change in the cell volume, in others, especially with a high red cell count, there is a great decrease in cell volume. A color index within normal limits is seldom found in this group, and the saturation index is usually well below normal. In this entire group only 4 patients, other than those suffering from pernicious anemia, had a mean corpuscular volume greater than 1. The clinical diagnoses were anemia due to infection of the arm following vaccination, cancer of the stomach, cancer of the colon and von Jaksch's anemia. The average red cell

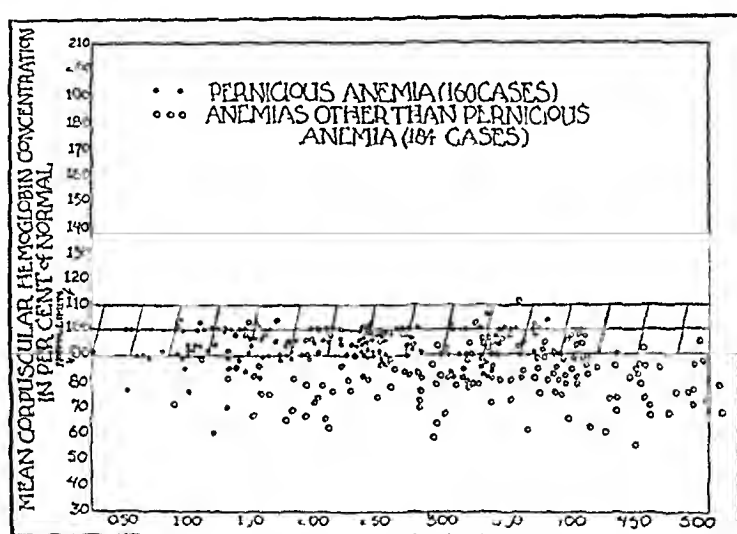


Fig 6—The mean corpuscular hemoglobin concentration in pernicious anemia contrasted with that in other types of anemia. The hemoglobin concentration is never above the normal limit.

count was 3.46 millions, the volume index 0.86, corresponding to a mean corpuscular volume of 78 cubic microns, the color index 0.77, indicating a mean corpuscular hemoglobin of 23.7 micromicrograms of hemoglobin per cell, and the saturation index 0.90, which is equivalent to a hemoglobin concentration of 30.1 per cent. The lowest volume index was 0.63, the lowest color index 0.37 and the lowest saturation index 0.60. The red cell count varied from 1.60 to 5.96 million.

During the period of this study 160 cases of pernicious anemia have been seen. The determinations in 20 patients with widely varying red cell counts are shown in table 6. The average count for the entire series was 1.85 millions, the volume index 1.43 (mean corpuscular volume, 132 cubic microns), the color index 1.31 (mean corpuscular hemoglobin, 40.4 micromicrograms), and the saturation index 0.91.

TABLE 6—*Determinations in Pernicious Anemia*

Red Blood Cells per Cu Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Hemoglobin				Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
	Hematocrit Reading, per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc.		Gm per 100 Cc.	Per Cent of Normal	Hemo globin Coefficient, Gm	Mean Corpuscular Hemoglobin, Micro grams			
Typical Determinations											
0.40	6.9	15	76	152	1.66	1.8	12	20.4	1.33	27.0	0.80
0.53	7.8	17	74	148	1.60	2.5	16	25.8	1.68	35.3	1.05
0.39	7.8	17	65	130	1.42	2.6	17	21.8	1.42	33.7	1.00
0.66	9.7	21	75	150	1.62	3.2	21	25.0	1.62	33.7	1.00
0.73	12.0	27	83	166	1.80	3.7	24	24.6	1.60	30.0	0.80
0.80	15.0	32	92	184	2.00	3.9	26	25.0	1.62	27.1	0.81
1.00	11.5	25	58	116	1.25	3.2	21	16.2	1.05	28.4	0.84
1.05	17.0	38	83	166	1.81	5.9	38	27.9	1.81	33.7	1.00
1.14	16.0	35	70	146	1.52	5.4	35	23.4	1.52	33.7	1.00
1.20	15.0	33	63	126	1.33	4.6	30	19.3	1.25	30.7	0.91
1.39	20.0	44	71	142	1.56	6.0	39	21.4	1.39	29.6	0.88
1.41	18.5	40	65	130	1.43	6.0	39	21.4	1.39	33.0	0.98
1.55	22.0	48	70	140	1.52	7.1	46	22.8	1.48	32.4	0.96
1.75	21.0	46	64	128	1.33	5.8	38	16.9	1.10	26.7	0.79
2.10	27.0	58	62	124	1.35	8.5	55	20.0	1.30	32.4	0.96
2.25	27.0	58	59	118	1.29	8.5	55	18.8	1.22	32.0	0.95
2.40	29.0	63	60	120	1.30	9.2	60	19.3	1.25	32.4	0.96
2.88	39.0	85	67	134	1.46	11.9	77	20.4	1.33	30.7	0.91
3.10	35.0	75	56	112	1.21	11.7	76	19.0	1.23	34.3	1.02
3.60	43.0	94	60	120	1.29	14.5	94	19.9	1.29	33.7	1.00
Summary of 160 cases											
1.85	25.0	53	66	132	1.43	7.4	48	20.2	1.31	30.7	0.91

TABLE 7—*Determinations in Anemia Due to a Quantitative Defect in Blood Formation*

Red Blood Cells per Cu Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Hemoglobin			Mean Corpuscular Hemoglobin, micrograms	Color Index	Saturation per Cent	Diagnosis
	Hematocrit Reading, per 100 Cc., in Cc.	Per Cent of Normal	Volume Coeffi- cient, Cc.		Gm per 100 Cc.	Per Cent of Normal	Hemo- globin Coefficient, Gm				
Typical Determinations											
1 19	14	31	47	94	4 62	30	15 4	30 8	1 00	32 4	Acute myeloid leukemia
1 32	14	31	46	92	4 94	32	15 9	31 8	1 03	33 5	Osteitis fibrosa cystica
1 61	15	30	46	92	3 54	23	11 5	23 1	0 75	25 0	Alcoholic leukemia
2 30	21	47	43	86	7 24	47	14 5	29 0	0 94	33 5	Leukemia
2 53	30	66	43	86	7 80	51*	15 2	30 4	0 99	26 0	Multiple myeloma
2 63	24	54	47	94	7 70	50	14 5	29 0	0 90	30 7	Monocyte leukemia
Summary											
2 10	20	43	47	94	6 60	39	14 3	28 6	0 93	30 4	Average in 6 cases

* Determination made by means of the hemoglobinometer

(mean corpuscular hemoglobin concentration, 30.7 per cent) The lowest volume index was 1.13 and the highest 2.24, the lowest color index was 0.80 and the highest 1.87. The saturation index was never over 1.00 beyond the limits of error.

The one constant feature of the blood in pernicious anemia is the macrocytosis, as shown by the increased volume index. In the active cases the mean cell volume is well increased although it tends to be higher with the relatively low counts. Sixty per cent of the cell counts in pernicious anemia are below 20 millions while only 14 per cent of the other types of anemia are below 20 millions. I have reported elsewhere¹⁹ the correlation of the gastric analysis and the macrocytosis of the red cells in the diagnosis of pernicious anemia. I have seen no

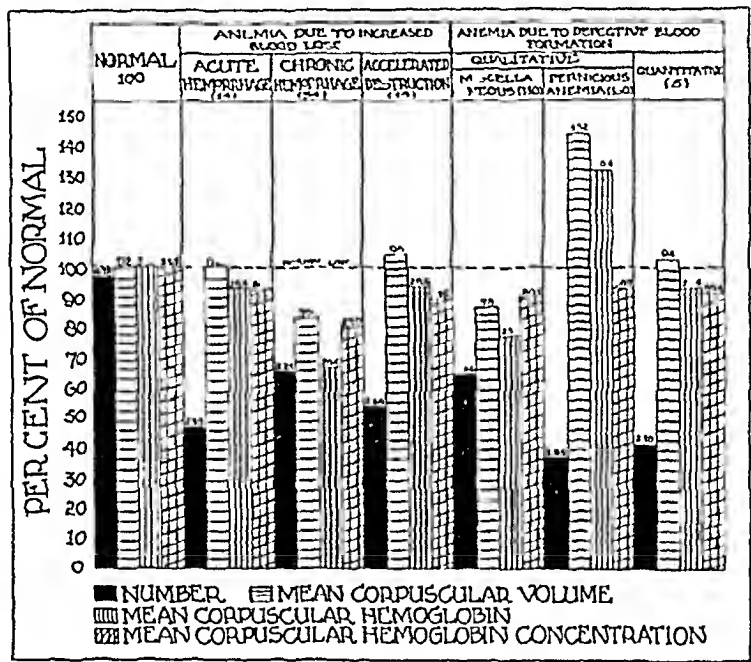


Fig 7—Erythrocyte constants (number, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) in the different clinical groups of anemia

untreated patient with an active case of pernicious anemia without a macrocytosis or with free hydrochloric acid in the gastric contents. A patient having a plus volume index with an achlorhydria practically without exception has pernicious anemia. The diagnosis of an untreated pernicious anemia in the absence of these two criteria is always open to question. On the other hand, macrocytosis is seldom seen except in pernicious anemia. Exceptions are seen in the acute anemia of pregnancy, some parasitic anemias and the hemolytic anemias due to hemolytic jaundice and to toxins.

¹⁹ Haden, R. L. Macrocytosis of the Erythrocytes and Achlorhydria in Pernicious Anemia, J. A. M. A. 98:202 (Jan 16) 1932.

TABLE 8—*Determinations in Polycythemia*

Red Blood Cells per Cu Min, Millions	Packed Red Cells			Mean Corpuscular			Hemoglobin			Mean Corpuscular Hemoglobin		
	Hematocrit Reading per 100 Cc, in Cc	Per Cent of Normal	Volume Coefficient, Cc	Volume, Cubic Microns	Volume Index	Gm per 100 Cc	Per Cent of Normal	Hemo globin Coefficient, Gm	Corpuscular Hemoglobin, Micro	Color Index	Saturation Index	Mean Corpuscular Hemoglobin Concentration, per Cent
6.09	52	113	42	84	0.92	18.79	122*	15.4	30.8	1.00	1.09	36.5
6.12	58	126	47	94	1.03	16.8	109*	13.6	27.2	0.88	0.87	29.3
6.90	66	114	48	96	1.04	21.6	140*	15.5	31.0	1.01	0.97	32.7
8.16	74	160	45	90	0.98	24.6	160	14.9	29.8	0.98	1.00	33.7
9.60	74	160	38	76	0.83	22.8	148	12.0	24.0	0.78	0.93	31.4
					Summary of 5 cases							
7.37	65	141	44	88	0.96	20.9	136	14.2	28.4	0.92		32.7

* Determination made by means of the hemoglobinometer

TABLE 9—*Summary of Determinations in Four Hundred and Forty-Four Cases*

Group	No	Red Blood Cells per Cu Min, Millions			Packed Red Cells			Mean Corpuscular			Hemoglobin			Mean Corpuscular Hemoglobin		
		Hematocrit Reading per 100 Cc, in Cc	Per Cent of Normal	Volume Coefficient, Cc	Volume, Cubic Microns	Volume Index	Gm per 100 Cc	Per Cent of Normal	Hemo globin Coefficient, Gm	Corpuscular Hemoglobin, Micro	Color Index	Saturation Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Color Index	Saturation Index	Mean Corpuscular Hemoglobin Concentration, per Cent
Normal	100	4.78	33.7	46	92	1.00	14.8	95	15.4	30.8	1.00	1.00	33.7	1.00		33.7
Acute hemorrhage	14	2.33	22.0	47	92	1.00	6.6	43	14.2	28.1	0.92	0.92	30.7	0.92		30.7
Chronic hemorrhage	34	3.25	25.0	38	76	0.83	6.6	43	10.2	20.4	0.66	0.66	27.0	0.66		27.0
Accelerated destruction	15	2.69	25.0	48	56	1.04	7.7	50	14.3	28.6	0.93	0.93	29.7	0.93		29.7
Defective formation (qualitative)	110	3.46	27.0	39	78	0.86	8.2	53	11.9	23.7	0.77	0.77	30.1	0.77		30.1
Pernicious anemia	160	1.85	23.0	53	132	1.43	7.4	48	20.2	40.4	1.31	1.31	30.7	1.31		30.7
Defective formation (quantitative)	6	2.10	20.0	43	94	1.02	6.0	39	14.3	28.6	0.93	0.93	30.1	0.93		30.1
Polycythemia	5	7.37	65.0	44	88	0.96	20.9	136	11.2	28.4	0.92	0.92	32.7	0.92		32.7

The anemias due to a quantitative defect in blood formation are relatively few. The group that I have studied are summarized in table 7. Here the cell volume and hemoglobin content are relatively normal as one would expect. It is always difficult to know just what cases to put in this group. In leukemia, while there is a decrease in red cell forming tissue by the infiltration, there may be also a depression of bone marrow formation secondary to the toxemia characteristic of the disease.

The determinations in a small group of polycythemia vera are shown in table 8. The cell volume was normal in 4 cases. In one with a count of 960 millions, the volume index was 0.83 and the color index was 0.78. In the others the color index was relatively normal and the saturation index was normal in all. It is probable that the percentage by volume of packed cells cannot exceed 75, therefore if the cell count is above 750 millions, the mean corpuscular volume necessarily decreases.

The determinations in the 444 cases reported here are summarized in table 9, and in figures 4, 5, 6 and 7. From the standpoint of classification the important points are

1. There is a relatively slight change in mean cell volume and hemoglobin content in the acute anemia of hemorrhage or in quantitative defects in blood formation. Here there is a decrease in the number of cells, but the cells remaining are relatively normal.

2. There is a marked decrease in cell volume and hemoglobin content with long-continued mechanical blood loss. As the bone marrow is depleted, the cells become smaller with a low hemoglobin content.

3. In anemia due to accelerated blood destruction there is a tendency to macrocytosis. Most of the cases in this group show an increase in reticulocytes, which are larger than normal, hence the mean cell volume is greater than normal. This is not a constant observation, however.

4. In pernicious anemia macrocytosis is constant and marked.

5. In polycythemia the cell volume is unchanged until the count is high at which time the cells become smaller.

VALUE OF THE VOLUME AND HEMOGLOBIN CONTENT IN PROGNOSIS

In pernicious anemia a persistence of macrocytosis in spite of adequate treatment is a very unfavorable sign, since the macrocytosis is evidence of a lack of some principle necessary for normal blood formation. This is an unusual observation, but is made occasionally.

In other types of anemia the greater the decrease in average cell volume the greater is the depletion of bone marrow and the longer the

time required for the return of the blood to normal. For instance, one expects more rapid and satisfactory results from treatment in a patient with a cell count of 30 millions, a volume index of 1.00 and a hemoglobin content of 30 per cent than in a patient with the same

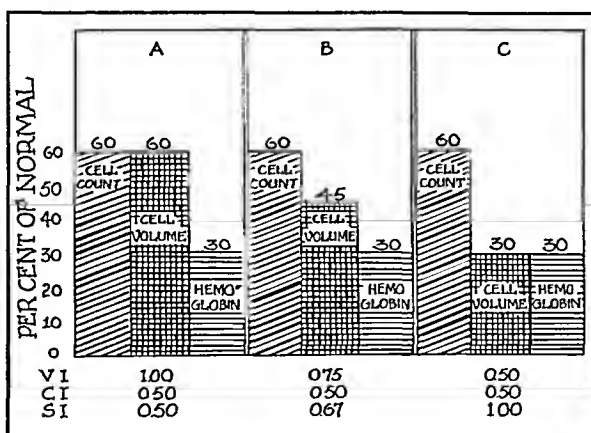


Fig 8—Relation of hemoglobin to cell volume with constant red cell count and hemoglobin but a varying volume of packed cells. In *A* the red cells are of normal size and half filled with hemoglobin, so that they have only to be filled with hemoglobin in order to return to normal, in *B* the cells are three-fourths normal size and two-thirds filled with hemoglobin, in *C* the cells are only half the normal size, but are filled with hemoglobin, so that both the cell mass and the hemoglobin must be increased to return to normal.

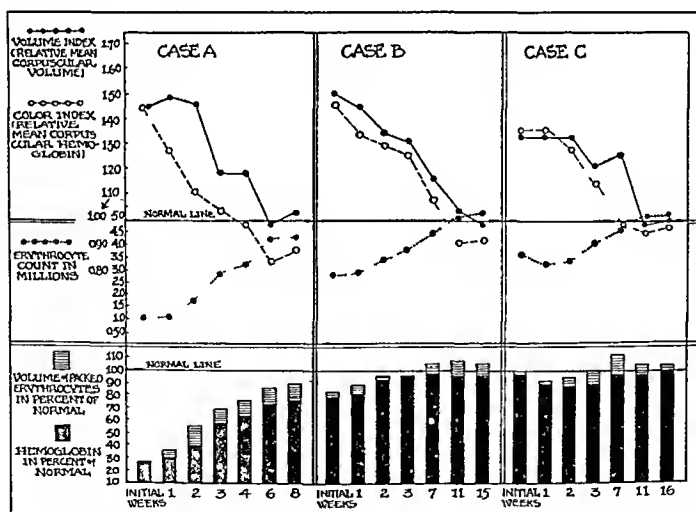


Fig 9—Changes in erythrocytes in three patients with pernicious anemia who have had adequate liver treatment. Note the simultaneous return to the normal line of the count and mean corpuscular volume.

cell count and hemoglobin content but with a volume index of 0.65. There are two reasons for this. The small cells indicate marked bone marrow depletion and hence a more serious state of the blood-forming tissue, and the hemoglobin cannot be increased until the cell volume is

TABLE 11—*Determinations in Patients with Pernicious Anemia Inadequately or Not Treated with Liver*

Case Weeks	Red Blood Cells per Cu Mm., millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Hemoglobin			Mean Corpuscular Hemoglobin, micrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index		
		Hematocrit Reading, in Cc	Per Cent of Normal	Volume Coefficient, Cc		Gm per 100 Cc	Per Cent of Normal	Hemo globin Coefficient, Gm						
D	0	0.69	9.7	21	70	140	1.52	3.08	20	22.3	44.6	1.45	32.0	0.95
	2	1.00	11.5	25	58	116	1.25	2.93	19	14.6	29.2	0.95	26.3	0.78
	3	1.62	21.0	46	65	130	1.42	5.85	38	18.0	36.0	1.17	27.9	0.82
	4	2.03	23.0	50	58	116	1.24	7.10	46	17.5	35.0	1.14	31.0	0.92
	6	2.82	37.0	80	63	126	1.37	10.70	67	17.7	35.4	1.15	28.3	0.81
	65	2.51	32.0	70	64	128	1.40	9.55	62	19.0	38.0	1.23	30.0	0.89
I	0	2.40	33.0	71	68	137	1.49	10.05	68	21.9	43.8	1.42	32.4	0.96
	12	3.66	40.0	87	55	109	1.19	11.55	75	15.9	31.8	1.03	29.0	0.86
	16	3.72	44.0	96	60	120	1.30	12.15	82	16.1	32.2	1.05	27.9	0.82
	22	3.32	46.0	100	69	138	1.50	12.61	82	19.1	38.2	1.24	27.9	0.82
	20	2.52	35.0	75	68	136	1.48	11.22	73	22.2	44.4	1.44	30.0	0.98
	30	2.42	38.5	83	78	157	1.71	12.31	80	25.4	50.8	1.65	32.4	0.96
	46	2.60	32.0	70	62	124	1.34	10.70	67	19.7	39.4	1.18	32.4	0.96
	60	2.94	42.0	92	71	143	1.56	15.21	86	22.5	45.0	1.46	31.4	0.93
T	0	1.83	25.0	54	67	134	1.46	7.40	48	20.2	40.4	1.30	30.0	0.89
	1	3.42	38.5	84	56	112	1.22	12.15	79	18.3	36.7	1.16	32.7	0.97
	8	3.31	30.0	65	45	91	0.99	10.00	65	15.3	30.5	0.99	33.7	1.00
	12	2.50	29.0	63	58	116	1.26	8.95	58	18.4	36.7	1.16	32.0	0.97
	20	3.12	32.0	70	52	104	1.13	11.10	72	18.4	36.7	1.16	34.7	1.03
	30	2.70	36.0	77	66	132	1.43	11.10	72	20.5	41.0	1.33	31.7	0.94
	42	2.65	32.0	69	60	120	1.30	10.05	66	20.8	41.6	1.35	32.7	0.97
	62	1.06	23.0	50	111	222	2.40	7.25	47	34.5	69.0	2.24	31.7	0.94
	63	2.06	30.0	65	71	142	1.55	9.55	62	22.7	45.5	1.48	32.7	0.97
	65	3.30	36.0	77	55	110	1.20	11.40	74	18.3	36.7	1.16	32.7	0.97
	69	4.02	44.0	96	55	110	1.20	14.00	91	17.6	37.1	1.14	32.0	0.95
	81	4.50	41.0	90	46	92	1.00	12.31	90	13.7	27.4	0.89	30.0	0.89

increased The formation of stroma, or hemoglobin-carrying substance, must precede the formation of hemoglobin This point is illustrated in figure 8

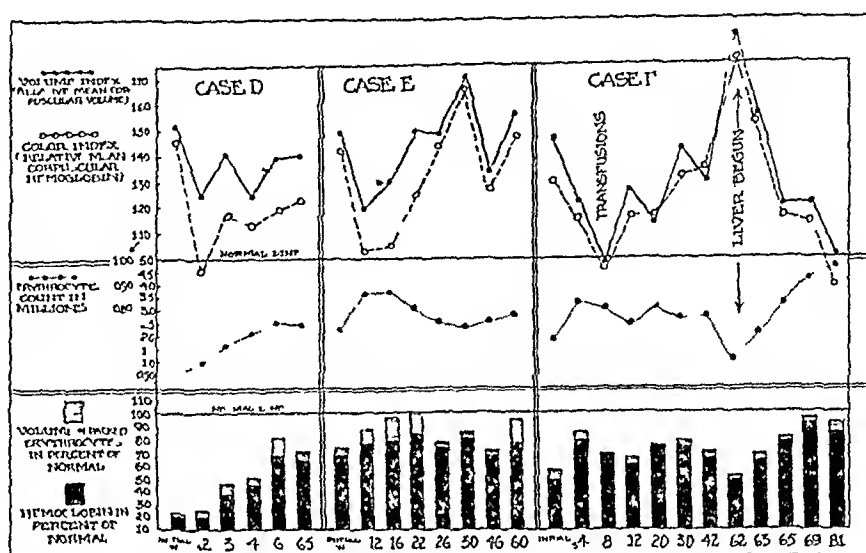


Fig 10—Changes in erythrocytes in three patients with pernicious anemia who have had inadequate or no liver treatment Note that the cell count remains below normal and the mean corpuscular volume constantly above the normal line

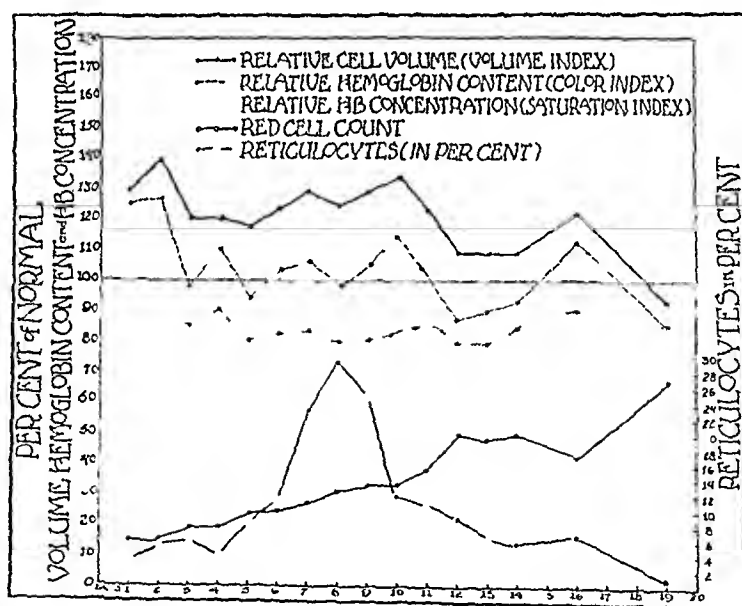


Fig 11—Daily determinations of the erythrocyte constant in a patient with pernicious anemia who has had adequate liver treatment

THE VOLUME AND HEMOGLOBIN CONTENT AS AN INDEX OF THERAPY

With the newer methods of treatment for pernicious anemia the blood will return to normal As the red cell count rises to normal, the mean corpuscular volume indicated by the volume index falls, so the

TABLE 12—Daily Determinations in a Patient with Pernicious Anemia Adequately Treated with Liver

Days	Packed Red Cells				Mean Corpuscular Volume, Cubic Microns	Hemoglobin				Mean Corpuscular Hemoglobin, Micrograms	Color Index	Saturation Index	Reticulo cytes
	Red Blood Cells per Cu Mm., per 100 Ce.	Hematocrit Reading in Ce.		Per Cent of Normal		Volume Coeffi. of Cent.	Gm per 100 Ce	Per Cent of Normal	Hemo globin Coefficient, Gm				
		Hemo globin	Per Cent of Normal										
0	0.81	9.7	21	60	120	3.08	20	20.8	41.6	1.26	0.95	3.6	
1	0.76	9.7	21	67	134	2.93	19	22.3	44.6	1.27	0.90	5.0	
2	0.97	10.2	22	56	113	2.93	19	15.1	30.2	0.98	0.86	6.0	
3	0.94	10.5	23	50	112	3.24	21	17.1	34.2	1.11	0.91	4.2	
4	1.14	12.0	27	55	109	3.40	22	14.8	29.6	0.96	0.81	8.4	
5	1.27	14.0	31	57	114	3.86	26	15.7	31.4	1.04	0.83	11.2	
6	1.34	16.0	35	60	120	4.47	29	16.5	33.0	1.07	0.83	23.1	
7	1.58	18.5	40	57	115	4.94	32	15.4	30.8	1.00	0.80	29.8	
8	1.65	19.5	43	60	125	5.40	35	16.1	32.2	1.06	0.81	25.0	
9	1.67	21.5	45	62	124	5.85	38	17.7	35.4	1.15	0.84	12.0	
10	1.93	22.0	48	57	114	6.16	40	15.9	31.8	1.03	0.86	11.0	
11	2.56	26.0	56	55	111	6.95	45	13.7	27.4	0.89	0.80	9.0	
12	2.45	25.0	54	55	111	6.95	45	14.0	28.0	0.91	0.80	6.0	
13	2.57	26.0	56	55	111	7.40	48	29.0	58.0	0.94	0.85	0.2	
15	2.19	26.0	56	57	114	8.00	52	18.1	36.2	1.18	0.92	7.0	
18	3.43	30.0	65	43	86	8.95	58	12.9	25.8	0.84	0.86	1.0	
24	3.33	34.0	73	55	111	10.02	65	14.9	29.8	0.97	0.89	1.0	
26	3.65	36.0	77	48	97	10.80	70	14.8	29.6	0.96	0.90	1.0	

TABLE 13—Determinations in a Patient with Simple Actinolytic Anemia Adequately Treated with Iron

Weeks	Packed Red Cells				Mean Corpus- cular Volume, Cubic Microns	Hemoglobin			Mean Corpuscular Hemoglobin, Micro- grams	Color Index	Mean Corpuscular Hemoglobin Concen- tration, per Cent	Saturation Index
	Red Blood Cells per Cu Mm., Millions	Hematoerit		Gm per 100 Cc		Per Cent of Normal	Hemo- globin Coefficient, Gm					
		Reading per 100 Cc, in Cc	Volume Coefficient, Cc									
0	5.02	35	66	32	64	7.55	49	7.55	15.0	0.49	23.6	0.70
1	5.95	41	89	35	70	9.40	61	8.00	16.0	0.52	22.6	0.67
2	5.80	42	91	36	72	10.95	71	9.40	18.8	0.61	26.3	0.78
3	6.16	46	100	37	74	11.70	78	9.70	19.4	0.63	26.3	0.78
4	5.63	46	100	41	82	11.70	78	10.61	21.2	0.69	26.3	0.78
5	5.66	48	104	42	84	14.97	84	11.40	22.8	0.74	28.3	0.83
6	0.00	50	109	31	62	14.00	91	11.70	23.4	0.76	28.3	0.83
7	5.87	48	104	41	82	14.00	91	11.85	23.7	0.77	29.3	0.87
9	5.66	49	106	44	88	14.00	91	12.50	25.0	0.81	29.3	0.87
11	5.56	48	104	43	86	14.00	91	12.35	24.7	0.80	29.6	0.88
16	5.27	45	97	42	84	14.00	91	13.25	27.5	0.86	31.4	0.93

lines indicating these two factors converge to a point on the base line. No patient with pernicious anemia is adequately and satisfactorily treated until the volume index has returned to normal. The aim of treatment is the relief from the anemia and the prevention of subacute combined degeneration of the spinal cord. The persistence of the anemia or the development of a cord lesion is the best of evidence that the deficiency responsible for the disease is not properly supplied. Since the advent of liver therapy, patients have been constantly seen who have taken enough liver to improve the anemia but not enough to return the blood to normal. In such patients a macrocytosis persists and usually a cord lesion develops during the period of treatment.

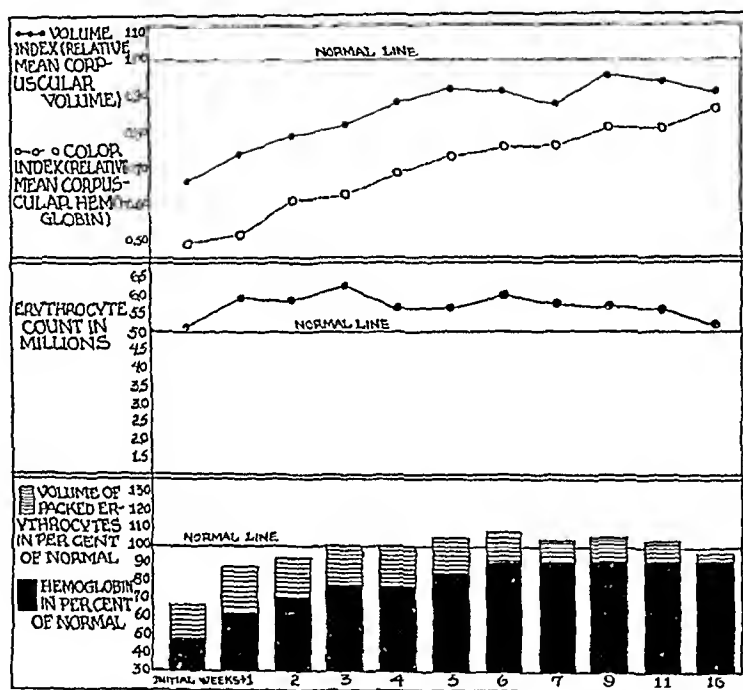


Fig 12—Changes in erythrocytes in a patient with simple achlorhydric anemia treated only with Bland's mass pills (60 grams [38 Gm.] daily). Note the relative constancy of the count while there is a gradual increase in the mean corpuscular volume. The cell mass increases greatly and is finally almost completely filled with hemoglobin.

In a general way the color index follows the volume index, but the color index may fall to normal with a persistence of the macrocytosis.

In table 10 are shown the determinations in a group of patients who showed the characteristic response to adequate liver therapy. This is illustrated in figure 9. The determinations in a group of patients who did not receive liver therapy or who received insufficient liver therapy are shown in table 11 and figure 10. The determinations in a single patient with daily blood studies are shown in table 12 and figure 11. In the case of every patient suffering from pernicious anemia a care-

ful blood study should be made at regular intervals to see that the volume index has returned to normal and has remained normal

In other types of anemia the aim of treatment is also to return the blood to normal. Here also careful studies of cell volume and size are valuable as an index of treatment. In simple achlorhydric anemia and other types of anemia that respond to adequate iron therapy, a study of the cell volume may give some interesting information concerning the action of iron in such conditions. The therapeutic action of iron in anemia has been related largely to the hemoglobin. In table 13 and figure 12 are shown the successive observations on the blood in a patient who received adequate iron therapy. There was a great increase in the volume of packed cells as well as in hemoglobin. These data would indicate that iron causes an increase in stroma as well as in hemoglobin.

SUMMARY

1 The accurate determination of the volume, hemoglobin content and hemoglobin concentrations of the erythrocyte is a relatively simple procedure and should be carried out in every case of anemia that requires careful study.

2 The results are best expressed as indexes rather than in absolute figures. The indexes express the absolute values relative to normal.

3 In normal men and women the indexes are always within the limits of normal (0.90 and 1.10).

4 Every case of anemia that warrants thorough study should be classified on the basis of the number, the volume and the hemoglobin content of the red blood cells.

5 A simple classification and terminology on the foregoing basis is suggested.

6 The typical determinations in different clinical groups of anemia are reported.

7 In the case of acute mechanical blood loss there is a change in the number of cells only; in chronic loss the cells become progressively smaller, with a low hemoglobin content.

8 If the anemia is due to accelerated destruction, the mean cell volume tends to increase since the reticulocytes are usually larger than normal.

9 With decreased blood formation the determinations are very variable. The mean cell volume and hemoglobin content are seldom greater than normal except in pernicious anemia.

10 In pernicious anemia an increase in volume and hemoglobin content is the most characteristic observation on the blood.

11 The volume and hemoglobin content are important aids in prognosis

12 In pernicious anemia the mean volume of the erythrocyte is the best index in treatment. If the patient is adequately treated, the mean cell volume returns to normal.

13 In the treatment for other types of anemia the volume and hemoglobin content of the red cell are valuable aids in treatment.

PRIMARY CANCER OF THE LUNG

A CLINICAL AND PATHOLOGIC SURVEY OF FIFTY CASES

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The relative frequency and increasing tendency toward the occurrence of primary cancer of the lung has prompted me to make the following correlation. The clinical data was obtained through the cooperation of the various medical and roentgenologic departments. In reviewing the autopsy records from October, 1929, to November, 1930, 50 cases of primary cancer of the lung were found. The total number of autopsies made during this period was 3,064, the relative frequency of cancer of the lung being, therefore, 1.5 per cent. Deducting the number of autopsies made on persons 30 years of age or under left 2,209. The incidence of cancer of the lung in this group over 30 years was therefore 2.26 per cent.

I shall first consider the clinical aspect of this disease. In an endeavor to find some of the possible etiologic factors, the following observations were made:

Of the group studied, 78 per cent were males and 22 per cent females. From the autopsy records during this period the ratio was 52.5 per cent males to 47.5 per cent females, practically an equal division. The variation in age in the group of 50 patients was from 37 to 77 years, the average being 50.7. Four per cent were between 30 and 40 years of age, 14 per cent between 40 and 50, 48 per cent between 50 and 60, 24 per cent between 60 and 70 and 10 per cent between 70 and 80, 72 per cent of this group were smokers.

A study of environment or occupation proved of little significance. The patients were all born either in Austria or in one of the adjacent countries, and were all from the working class. The number of years spent in large or small communities, factory centers, farming districts, etc., was not obtainable from the existing records. The occupations were varied, and were thirty in number. In only one patient was a history of a chronic cough as a result of his occupation noted. This patient was an upholsterer. The largest number in any one occupation was among the women, 6 being domestic servants. Of the 39 men only 5 could be said to have been subjected to more than the average

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amount of respiratory irritation, as far as their stated occupations were concerned. Irritating fumes of any sort, with the possible exception of tobacco, did not seem to play a rôle. In the family history the percentage of parents who died of cancer in any part of the body, or of diseases of the lung, was considered. In the past history previous pulmonary or pleural illnesses were noted. In 47 cases in which a family and past history was obtainable, the information given in table 1 was derived.

Of particular interest were the 4 patients in whose histories periodic attacks of high fever, irritating cough, expectoration and accompanying shortness of breath were noted. The expectoration in the early stages was generally small in amount, and increased appreciably as the fever decreased. The attacks usually lasted from two to six weeks, and the patients had been treated in many hospitals. No tubercle bacilli were ever found. The intervals of comparatively good health

TABLE 1—*History*

	Per Cent
Family history	
Parents who died of cancer	15
Parents who died of pulmonary infection	24
Past history	
Grip, pneumonia, upper respiratory infection	17
Bronchitic or asthmatic attacks	15
Recurrent bronchial stenosis	8
Pleurisy	6
Tuberculous infection	2
Total	48

varied from six months to two years, and sometimes even longer. The attacks lasted over a period of several years, one case dating back as far as 1910. These cases were suggestive of the clinical picture of recurrent bronchial stenosis of an inflammatory nature. At autopsy, in these cases, enlarged chronically inflamed hilar glands were found, more often left-sided, causing a compression of the bronchial wall, or the bronchial wall itself showed chronic inflammatory changes with a resulting narrowing of its lumen.

In the present illness, the range of time from the appearance of the first symptom to the day of death was from two years to one day, the average being seven months and twenty-four days. A tabulation of initial symptoms in the present illness is given in table 2.

A grouping of certain specialized symptoms may be observed in table 3. Loss of weight was one of the frequent complaints, and in many cases was marked. In most cases the early cough was dry, irritative and nonproductive, often coming on in severe attacks. As the illness progressed, the cough became productive and purulent in some cases. The amount of sputum varied periodically, depending on the degree of

bronchial stenosis and on the degree of peripheral bronchiectasis, pneumonic infiltrate or abscess formation. It is interesting to note the high percentage of initial symptoms that were the result of metastases rather than the result of the primary growth. This shows the impossibility of an early diagnosis in a large percentage of the cases.

In considering the physical examination of the chest, I shall not attempt to tabulate the findings because of their great variability, individually or collectively, from day to day or from week to week. In 3 cases no abnormal pulmonary findings were noted. In 2 of these cases early cerebral metastases played the predominant rôle, and no pathologic pulmonary findings were noted on the patients' admission to

TABLE 2—*Initial Symptoms*

	Per Cent
Lung Attacks of coughing	12
Shortness of breath	14
Bloody sputum	4
Bronchitis	10
Pain in chest	4
Pleurisy	12
Nervous Cerebral	14
Peripheral	6
Hoarseness (recurrent nerve palsy)	8
Bone	6
Stomach	8
Uterine bleeding	2

TABLE 3—*Selected Symptoms*

No	Per Cent
15 Pleurisy	30
11 Bloody sputum	22
9 Hoarseness (recurrent nerve palsy)	18
3 Generalized pain in chest	6
3 Difficulty in swallowing	6
6 No symptoms in chest	12

the hospital. Later examinations of the chest were probably neglected owing to the lack of pulmonary symptoms. In the third case the patient had no pulmonary symptoms, and clinical attention was centered chiefly on the cervical and upper mediastinal glandular involvement. From this group of cases with negative findings one may turn to those in which examination revealed the signs of a moderate to a severe bronchitis or assimilated asthma, with an accompanying degree of emphysema. In cases with more advanced symptoms in the lung, some or all of the following signs were frequently found:

1 The presence of a venous collateral circulation across the anterior wall of the chest

2 The shrinkage of one side of the thoracic cage, with a decrease in the intercostal spaces and a varying degree of retraction of the supraclavicular fossa

- 3 A lesser respiratory movement on the shrunken side
- 4 Tracheal deviation toward the affected side
- 5 Dulness on percussion as the result of a tumor, atelectasis peripheral to a bronchial occlusion, an existing pneumonia or pleural exudate
- 6 Paravertebral dulness as a result of mediastinal involvement or hilar infiltration
- 7 Hyperresonance as a compensatory measure in the remaining normal or emphysematous lung tissue
- 8 Tympanitic resonance in patients with large cavity formation
- 9 A lesser degree of respiratory excursion, amounting to a paralysis and upward retraction of the diaphragm on the affected side
- 10 Every possible type of breathing or râle, depending on the existing condition of the underlying lung tissue and bronchial tubes
- 11 Frequently a pleural rub



Fig 1—Infiltrating process in the right upper lobe with multiple cavities. The trachea is toward the right. The esophageal obstruction is shown by barium sulphate filling. Hilar infiltration is seen. The roentgen diagnosis was the appearance of lung and esophagus is suggestive of bronchial neoplasm with involvement of the mediastinal glands. Autopsy showed carcinoma of the bronchus of the right upper lobe, first order.

In case of marked pleural effusion the bulging or fulness of the wall of the chest and the deviation of the trachea toward the opposite side overshadowed the tumor picture. These signs varied in number and in intensity, depending on the stage and location of the tumor. I think that at this time the greatest stress is to be laid on the great variability and changeability of the signs in the chest. This multiplicity and variation is due largely to the alternating degree of bronchial stenosis and its effect on the peripheral lung tissue. Therefore, the largest amount of information can be derived only by carefully recording the results of repeated examination of the chest. These findings on physical examination may prove a great diagnostic aid.

During hospitalization from a moderate to a severe degree of dyspnea was observed in 66 per cent of the cases, terminal dyspnea being omitted. Taken during the period of hospitalization the respiratory range often showed a marked flexibility. In several cases there was a variation of from twelve to fifteen respirations per minute, and in one case, a variation of twenty. This flexibility was largely dependent on the existing degree of bronchial stenosis. In some cases, however, the marked degree of cyanosis with accompanying rapid respiration was



Fig. 2—Rather sharp-bordered, fist-sized shadow in the right lower lobe. Medial upward fixation of the right side of the diaphragm. The roentgen diagnosis was probable neoplasm of the right lower lobe (*echinococcus cysticus*?). Autopsy showed carcinoma of the right inferior bronchus, second order.

due to pleural exudate or pressure exerted by mediastinal glands. In the latter group the cyanosis was more likely to be a constant factor and the respiratory rate persistently high. In a few cases during the course of the illness a marked drop in blood pressure was noted. At autopsy these cases showed a bilateral suprarenal involvement.

The period of hospitalization varied from one day to six months and twenty-one days, but the average was one month and fifteen days.

Among the laboratory data I shall first consider the roentgen observations. Roentgenography was found to be the most valuable laboratory

aid in making a correct diagnosis. X-ray plates or fluoroscopic examinations were made of the chest in 40 cases. Of the remaining patients 4 were too weak, and in 6 the metastatic foci presented the dominant symptom, in 2 of these the changes in the lungs were considered to be secondary to a primary growth elsewhere. The presence of a neoplasm was suspected in 72.5 per cent of the cases, if not from the first film, then from a series of films taken at intervals. In only 2 instances were the roentgenologists unable to rule out a tuberculous process. In both of these instances, however, a malignant process was also suspected. Both cases showed upper lobar cavitation.

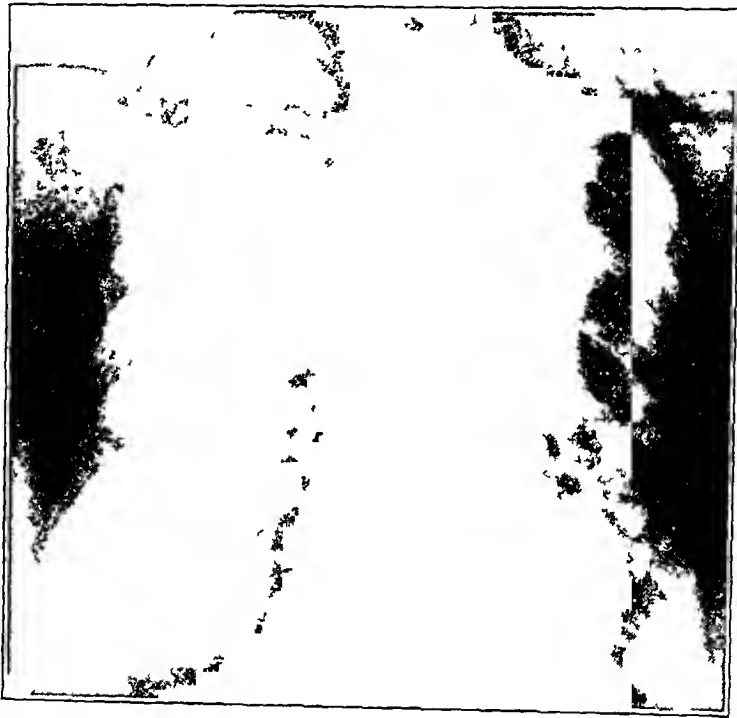


Fig 3—A large, unhomogeneous, not sharply bordered shadow extending into the upper left lung field from the hilar region. There is tracheal deviation toward the left. The left side of the diaphragm is high. (By fluoroscopy paradoxical respiration and paralysis of the left side of the diaphragm were demonstrated.) The roentgen diagnosis was probable bronchial carcinoma of the left lung with left-sided phrenic palsy from mediastinal involvement. Autopsy showed left superior bronchial carcinoma, second order.

Some of the findings that lead one to suspect the presence of a malignant process are

- 1 Shrinkage of the affected side
- 2 The presence of an infiltrating process, most often in the hilar region, showing a marked tendency toward peribronchial infiltration
- 3 The presence of a bronchial stenosis characterized by a partial or complete atelectasis of the affected portion of pulmonary tissue
- 4 Retraction of the heart and mediastinal contents toward the affected side
- 5 Upward retraction of the diaphragm on the affected side

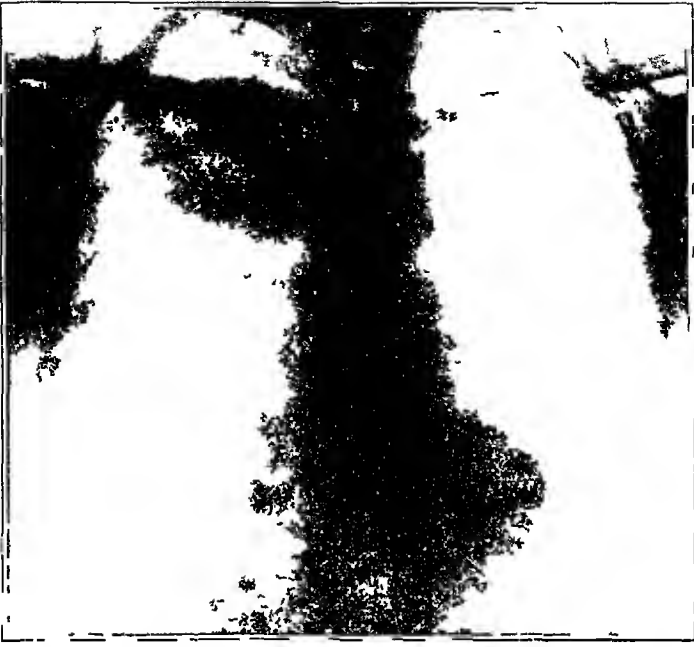


Fig 4—In right upper lobe a shadow the size of a child's fist, not sharply bordered and with finger-like offshoots, hilar infiltration on both sides The roentgen diagnosis was tumor of the bronchus (?) Autopsy showed right superior bronchial carcinoma, second order

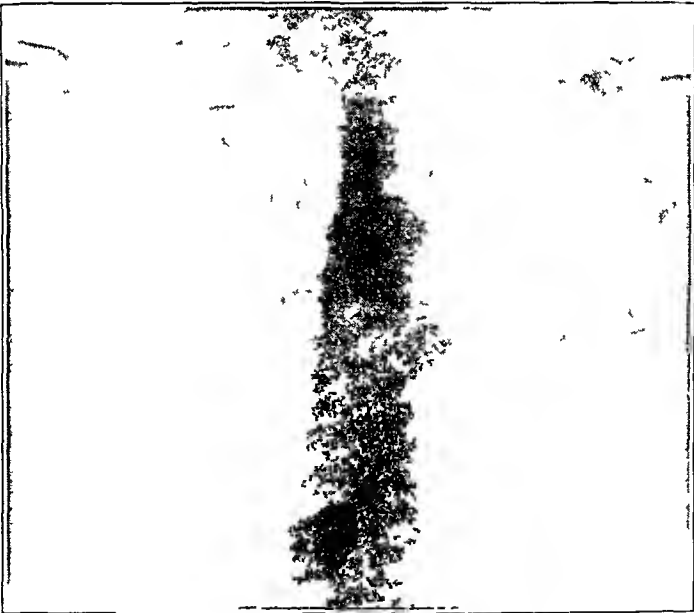


Fig 5—In left hilar region a shadow, not sharply bordered, with infiltrating bands extending into the left lung, mediastinum displaced somewhat toward the left The roentgen diagnosis was probable neoplasm of the bronchus of the left lung Autopsy showed carcinoma of the left bronchus extending to the entrance of both the superior and the inferior bronchus

6 In from 75 to 10 per cent, evidence of palsy of the phrenic nerve (more often left-sided), with paralysis of the corresponding side, and an accompanying paradoxical respiration

7 Widening of the mediastinal shadow

Figures 1 to 5, inclusive, demonstrate a few cases suggestive of a primary malignant process in the lung

In cases of suspected malignancy, the difficulty at times lies in making a diagnosis that differentiates between a primary tumor of the lung and a mediastinal tumor. This difficulty is more apt to arise when



Fig 6—Marked mediastinal involvement and comparatively little infiltration of lung tissue. A barium sulphate meal demonstrates esophageal obstruction. The roentgen diagnosis was mediastinal tumor with esophageal obstruction. Autopsy showed carcinoma of the right main bronchus.

the primary tumor is located either in a main bronchus or in the first portion of a bronchus of an upper lobe (figs 6 and 7). It may also arise in cases of tumor in a bronchus of the left inferior lobe because of the heart shadow covering the primarily affected area. The former group frequently metastasize very early to the mediastinum, showing a little hilar infiltration, which might readily be mistaken as secondary to a primary mediastinal tumor. Evidence of palsy of the phrenic nerve (in 75 per cent of this group) is strongly indicative of a malignant

process, as this condition rarely accompanies a tuberculous mediastinal involvement (figs 3 and 7)

In the remaining group the roentgen diagnosis was necessarily secondary, showing either extensive pleural exudate (15 per cent), atelectasis (7.5 per cent), abscess cavity formation (5 per cent), a pneumonic infiltrate (2.5 per cent) or a suggestive bronchiectasis (2.5 per cent)

Roentgenography was also of value in confirming the clinical diagnosis of early metastases to the bone. These were more frequently found in the region of the chest although occasionally in the extremities. Emphysema was a frequent secondary observation.



Fig 7—Mediastinal tumor, more developed on the left side. There is some bandlike infiltration toward the apex of the left lung. The left side of the diaphragm is very high. The roentgen diagnosis was (1) mediastinal tumor with phrenic palsy (?) and (2) bronchial carcinoma (?). Autopsy showed carcinoma of the beginning of the bronchus of the left superior lobe.

The bronchoscope was employed in only 3 cases. In 2 the diagnosis of bronchial carcinoma was made, and in 1 of these cases was verified by biopsy. The third case was diagnosed as one of mediastinal tumor because, on examination, the bronchial mucosa appeared normal and the existing stenosis of the left main bronchus seemed the result of pressure from the outside. The primary growth in this case was situated in the second order bronchus of the left superior lobe.

Iodized oil was not injected in any of the 50 cases. The Wassermann reaction was positive in 2. These patients gave a long-standing history of syphilis. The sputum was examined in 70 per cent of the patients. In a few the twenty-four hour specimen was observed and

measured. The quantity varied from a very small amount to 300 cc, the latter amount belonging to the group with large cavity or bronchiectatic formation. The amount varied according to the degree of bronchial stenosis present. In the stages of complete or almost complete bronchial occlusion there was little or no sputum. Increasing toxicity and a rise in temperature were accompanying factors. No mention was made of the sputum having a disagreeable odor. It varied from mucopurulent to purulent. Blood was noted in 16 per cent, tumor cells in 2 per cent and elastic fibers in 2 per cent, tubercle bacilli were absent in all cases.



Fig 8—Tumor infiltration at the beginning of the bronchus of the middle lobe and extending throughout the middle lobe. Several metastatic nodules are seen appearing on the surface of the right lower lobe. The lumen of the bronchus of the middle lobe is completely occluded.

A pleural puncture was performed in 18 per cent of the cases with the results shown in table 4. In 2 of the 4 cases reported as showing a hemorrhagic exudate, the first aspiration revealed a clear straw-colored fluid which later became hemorrhagic. The degree of anemia was slight during the early stages of the disease. As the metastatic involvement progressed, the anemia became more marked. A moderate leukocytosis with a corresponding increase in polymorphonuclear leukocytes was generally present. The principal clinical diagnoses are given in table 5.

The clinical course may be summarized as follows. Almost 80 per cent of the cases occurred in men, 50 per cent being between the ages of 50 and 60, 39 per cent of the patients died either from a cancer or of infection of the lung. Approximately 50 per cent of the patients gave a previous history of disease of the chest, a few histories being suggestive of recurrent attacks of bronchial stenosis. A study of occupation yielded little information. Perhaps 20 per cent of the patients could be said to have been subjected to more than the ordinary respiratory irritation aside from that caused by tobacco. Of interest is the fact that 44 per cent gave as their first symptom one that was not connected with the chest. 12 per cent went through the entire course of the illness

TABLE 4—*Clinical Observations on Pleural Puncture*

	Number of Cases
Hemorrhagic	4
Purulent	3
Clear straw colored	2
Tumor cells	1 (1 case ?)
Negative (tuberculin reaction)*	All
Specific gravity 1.018-1.022	
Culture Hemolytic streptococcus	1
Pneumococci	1

* Negative for tubercle bacilli

TABLE 5—*Clinical Diagnosis in Fifty Cases*

No	Per Cent
33 Primary pulmonary tumor (bronchial carcinoma in most cases)	66
7 Primary mediastinal tumor	14
3 Cerebral tumor (terminal pneumonia, 2)	6
2 Cardiac insufficiency, bronchitis, emphysema	4
1 Empyema	2
1 Sarcoma of uterus (metastasis to lung)	2
1 Carcinoma of ovary (metastasis to lung)	2
1 Chronic gangrenous pneumonia, cavitation	2
1 Exudative pleurisy, emphysema, bronchial pneumonia	2

without a pulmonary symptom. Blood-tinged sputum was observed in only 22 per cent, a fact that should warn one against a dismissal of the possibility of a malignant process in the absence of this finding. Hoarseness as a result of a recurrent nerve palsy was a rather common symptom and at times occurred early in the course of the illness. The left recurrent nerve is more apt to be involved than the right. Marked esophageal disturbance did not play a prominent rôle in this group, being noted in only 6 per cent.

Physical examination may reveal one or more of a large group of pathologic signs, and the best interpretation of these findings may be obtained by carefully repeated examinations. The gradual loss of weight, beginning cachexia and progressive anemia help one in diagnosing a malignant process. A marked degree of cachexia was more apt to be found in cases of advanced metastatic involvement. In those cases the supraclaviculars were frequently involved. Often, however, the



Fig 9—Whitish cancerous tissue at the entrance to the left main bronchus, extending along the left main bronchus and also infiltrating the surrounding lung tissue. More peripherally some of the lumina of dilated bronchi can be seen.



Fig 10—Following along the left main bronchus one observes the grayish-white tumor tissue at the entrance of the bronchus of the left superior lobe. Its lumen is almost entirely occluded, and the sectioned superior lobe, appearing very dark, is entirely atelectatic. On both sides at the beginning of the sectioned superior lobe bronchus, one sees a markedly enlarged, anthracotic lymph gland.

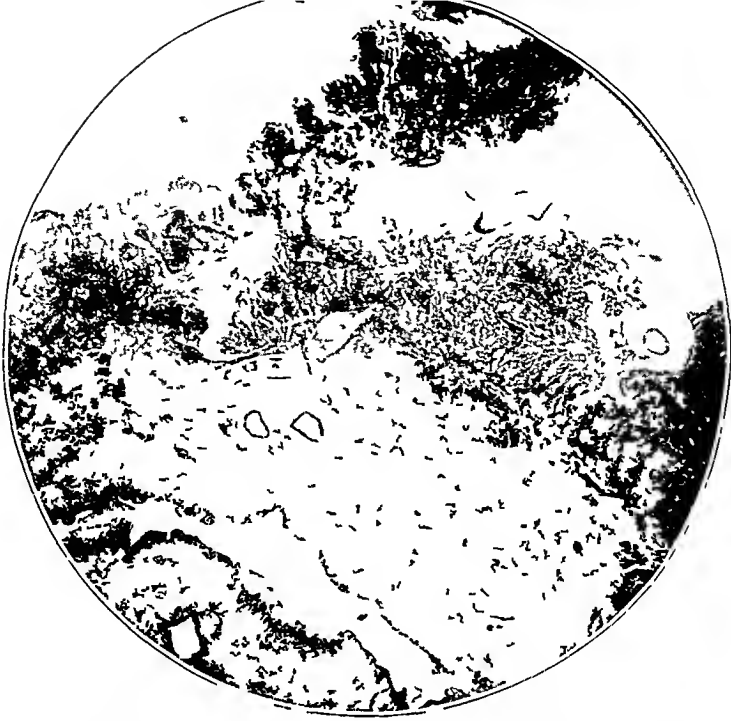


Fig 11—Tumor infiltration of the bronchial wall with polypoid growth into the lumen. A portion of bronchial cartilage is shown. The lower portion shows the chronically infiltrated lung tissue and a dilated bronchus with peribronchial leukocytic infiltration.



Fig 12—Normal appearing bronchi. The cut sections of the middle and lower lobes are entirely filled by diffuse grayish-white cancerous tissue.

patient did not show marked signs of inanition at autopsy, the skin, subcutaneous, and muscular tissues being well preserved

The laboratory observations, singly or collectively, may prove of great value if examinations are carefully and thoroughly carried out. In a goodly percentage of cases one can diagnose a probable primary mediastinal or pulmonary tumor by means of roentgenograms. The differentiation between these two conditions as to which is primary is sometimes impossible to make. In other cases, because of a pleural exudate, atelectasis, large abscess formation, bronchiectasis, etc., the

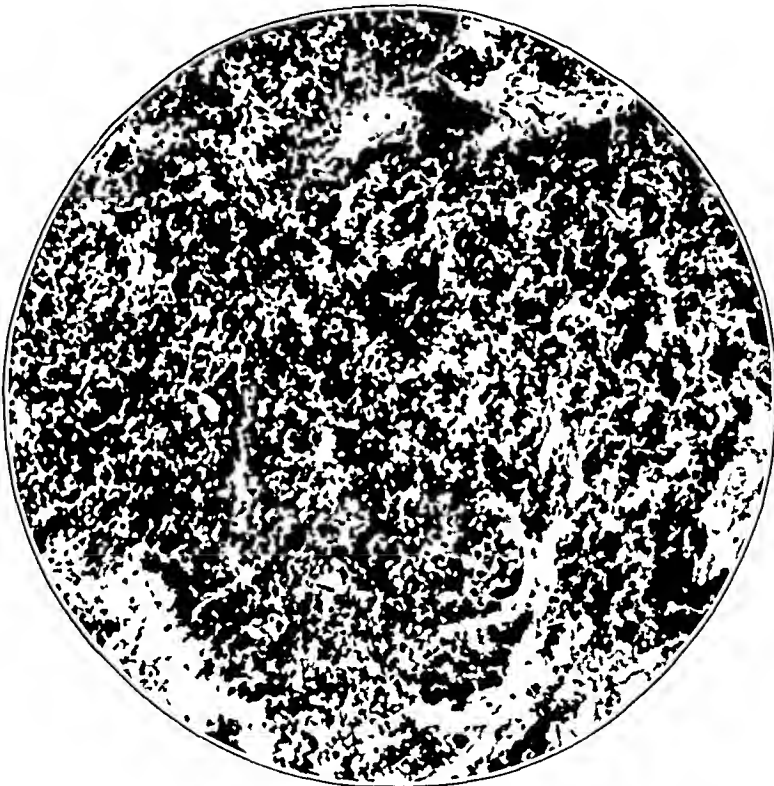


Fig 13—Small cell type of carcinoma showing the small cell proliferation almost solid in this view

diagnosis may be secondary. A series of roentgenograms taken over a period of time may disclose the condition, whereas one plate may not. Roentgenography also provides a possibility of diagnosing early metastases to the bone.

Although not used in this series, iodized oil may be of considerable aid in the diagnosis, particularly in differentiating between a congenital and an acquired type of bronchiectasis with an existing bronchial stenosis. One can readily see the great value of bronchoscopy as a diagnostic aid, especially in the early course of the disease. In cases in which an operation is questionable, one can, with bronchoscopy, determine the extent of the tumor infiltration toward the main bronchi.

The sputum may be of great diagnostic value when carefully collected as a twenty-four hour specimen and not as an occasional one to be sent to the laboratory to be examined for tubercle bacilli. So also would be repeated aspirations in the event of pleural exudate, whereas an isolated aspiration might provide little information.

A marked drop in blood pressure, together with gastric symptoms and increasing cachexia, is suggestive of suprarenal involvement. This condition is not infrequently seen in the later stages of the disease.

I shall now consider the pathologic observations. The location of the primary growth is shown in table 6. A bronchial stenosis was present at the site of the primary growth in all of the cases of bronchial carcinoma. In most cases the entire wall of the bronchus was infiltrated with tumor tissue, and the mucosa was ulcerated in part or entirely

TABLE 6—*Site of Primary Tumor in Fifty Cases*

	Right	Left	Total
Main bronchus	7	4	11
Bronchus of superior lobe	9	14	23
1st order	7	9	
2d order	2	3	
3d order		2	
Bronchus of middle lobe, 1st order	5		5
Bronchus of inferior lobe	3	6	9
1st order	2	4	
2d order	1		
3d order		2	
Alveolar cancer			2
Middle, inferior	1		
Superior		1	

at this point. In a few cases the tumor showed a marked tendency to spread along the bronchial wall for a considerable distance. In one case, for example, the primary growth started at the beginning of the bronchus of the middle lobe, and the tumor infiltration extended in the main bronchus and above the bifurcation as far as the upper border of the lower third of the tracheal wall. In a case of cancer of the right main bronchus the tumor was polypoid in appearance with a broad infiltrating base. This was the only case in which the infiltration was entirely confined to the wall of the bronchus with no pulmonary infiltration, and in which no metastases were found. In 52 per cent there was widening of the bronchial lumen peripheral to the stenosis. The picture presented by these dilated bronchi varied from a purulent bronchitis to a severe bronchiectasis. In the remaining cases the existing stenosis was not sufficient to cause more than a mild bronchitis in a few, while in others the bronchi were entirely destroyed by a tumor or abscess formation. In another small group the peripheral bronchi remained unchanged because of collapse of the lobe due to the presence of a pleural exudate. In 1 case, two primary growths were

found, one in the bronchus of the left superior lobe, second order and the other in the bronchus of the right inferior lobe, first order

The changes in the lung are shown in table 7 and in figures 8, 9, 10 and 11. Figure 11 shows typical changes in the lung in the presence of a malignant process. The small cell tumor invasion with infiltration of the bronchial wall and lumen, the existing bronchiectasis with peribronchial leukocytic infiltration and the chronic fibrotic infiltration of the remaining pulmonary tissue are all clearly brought out by this slide



Fig 14—Squamous cell type of carcinoma showing numerous horn pearls

In the 2 cases of alveolar carcinoma both lungs were infiltrated by tumor tissue, the primary side being almost entirely involved (fig 12)

The pleural observations are given in table 8 and the metastatic observations in table 9. Table 9 shows the high percentage of mediastinal involvement by the lymphatic route. Of special interest also is the high percentage of metastases to the bone and brain, mainly by the blood route. In 9 cases there was bilateral involvement of the suprarenal glands, and in 8 cases unilateral involvement. These conditions together represented 34 per cent. The unilateral cases were equally divided. Practically the same division held true in the case of the kidneys, 6 cases showing bilateral involvement and 5 cases unilateral. Of the unilateral cases, 3 were left-sided.

The pathologic diagnosis showed 48 cases of primary bronchial carcinoma, 1 of which revealed two primary tumors, and 2 cases, alveolar carcinoma. The types of carcinoma found were (1) small cell, 68 per cent (fig 13), (2) squamous cell (with or without horn

TABLE 7—*Observations on the Lung in Forty-Eight Cases of Bronchial Carcinoma*

	A ₁	A ₂	B ₁	B ₂	B ₃
Tumor infiltrate	10		37	7	
Metastases	2		6	8	3
Bronchial	2	1	1	3	1
Pneumonia Indurative	1		8	2	
Gangrenous	3		2		
Atelectases	2	4	4	6	
Pleural exudate	2		11		
No pleural exudate	2				
Large abscess	1		3		
Emphysema	1	1		5	10

A₁ Cancer of the stem bronchus (affected lung), 11 cases
A₂ Opposite lung
B₁ Cancer of bronchi within a lobe (affected lobe), 37 cases
B₂ Adjacent lobe
B₃ Opposite lung

TABLE 8—*Pleural Observations at Autopsy*

	Affected Side, per Cent	Free Side, per Cent
Adhesions	78	36
Tumor infiltration	16	
Metastases	20	8
Exudate	52	12
Clear straw colored	24	10
Hemorrhagic	10	
Purulent	18	2
Fibrinous pleurisy	6	2

TABLE 9—*Metastases in Fifty Cases*

	Per Cent		Per Cent
Mediastinum	78	Thyroid	8
Bone	38	Skin spleen	4
Liver, suprarenals	34	Stomach, bladder	
Lung	28	Omentum muscle	
Kidneys	22	Bronchi, intestines	2
Cervical glands	20	Seminal vesicles	
Brain, pleura		Ureter, uterus	
Pericardium	12	Peritoneal glands	2
Myocardium	10	Superior vena cava	
Peritoneum		Submaxillary glands	
Retropertoneal glands		Spinal cord	
Pancreas			

pearls), 20 per cent (figs 14 and 15), (3) adenocarcinoma, 8 per cent (fig 16), and (4) alveolar carcinoma, 4 per cent (fig 17)

A summary of the pathologic observations is as follows. There is an equal tendency to tumor formation in either lung, 46 per cent occurred in the upper lobes as compared with 28 per cent in the middle and lower lobes, 76 per cent were found in the right or left main bronchi or in the first portion of the bronchi of the main lobe. The

primary growths situated in the main bronchi metastasize to the mediastinal lymph nodes in a very early stage and are a little slower to metastasize by the blood stream. A varying degree of bronchial stenosis is always present in cases of bronchial carcinoma, and is often accompanied by a peripheral bronchiectasis or, in a few cases, peripheral abscess formation. Atelectasis as a result of bronchial stenosis, tumor infiltration or pleural exudate of the involved or adjacent lung is a frequent finding. Various pneumonic changes are often present, chronic induration being the more frequent type in the affected lobe. Emphysema may be found in the adjacent lobe or in the opposite lung.

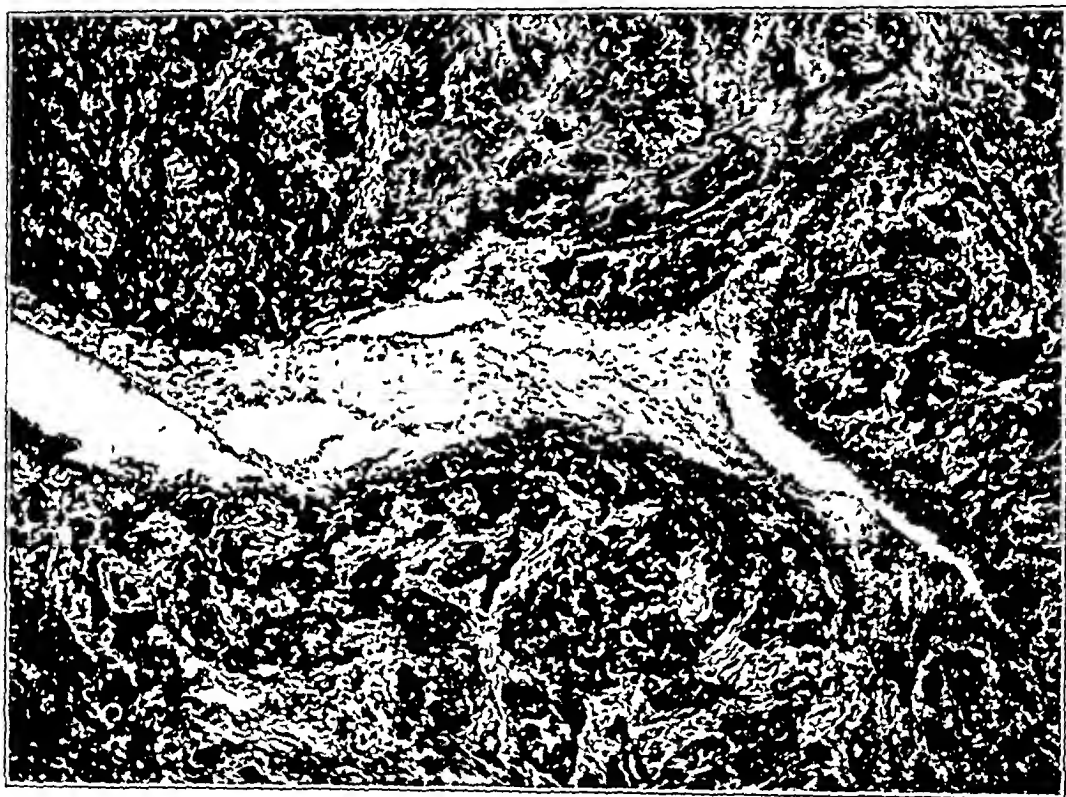


Fig. 15—Squamous cell type of carcinoma without horn pearl formation. The bronchial lumen is almost closed. A portion of bronchial cartilage is seen in the lower border.

In a few cases enlarged, chronically inflamed lymph glands were found around the hilar region as evidence of a long-standing or previous inflammatory condition. Pleural adhesions were commonly present, and almost 80 per cent of the patients had adhesions on the primary side, these being the result of an old inflammatory pleurisy, inflammatory changes during the present illness or tumor infiltration or metastasis. A pleural exudate was present in 52 per cent, while a hemorrhagic exudate was present in only 10 per cent. Tumor infiltration and metastasis to the pleura occurred in 36 per cent on the primary



Fig 16 Adenocarcinoma, the upper portion is bronchial cartilage and the remainder glandular proliferation with considerable mucus in the lumen

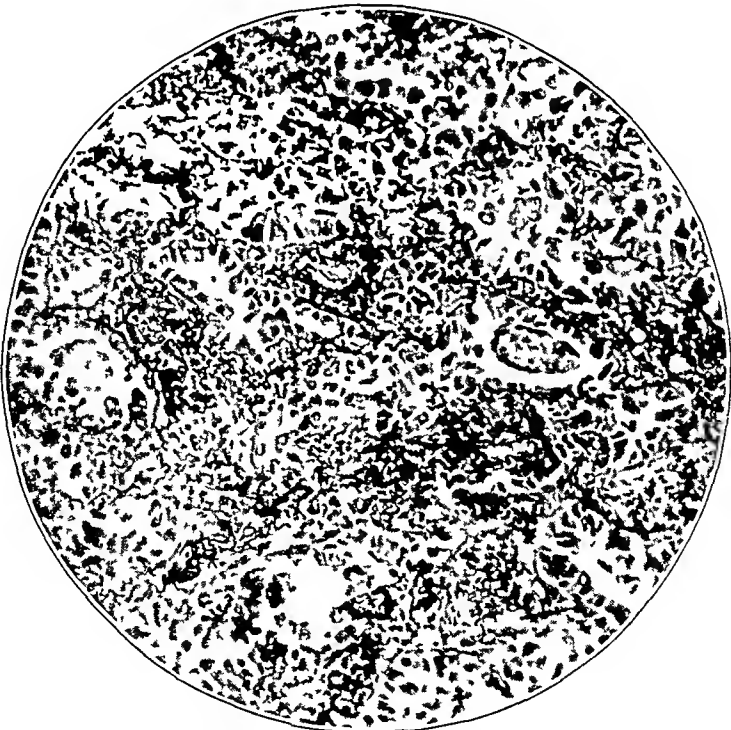


Fig 17 —Alveolar type of carcinoma, a special stain has been used to bring out the alveolar structure Enlargement and proliferation of the alveolar cells are readily seen

side. This shows the relative infrequency of a hemorrhagic exudate even in the presence of invasion by a tumor.

Pulmonary carcinomas are in most cases rather rapidly infiltrating tumors, tending to metastasize early by both the lymphatic and blood routes. Mediastinal nodes were involved in almost 80 per cent of the cases. These tumors show a marked tendency toward metastases to the bone, cerebrum, liver and suprarenals. In 3 cases the cerebral metastases were the only ones found. In 1 case the tumor was confined to the bronchus with no pulmonary or mediastinal involvement. In 3 cases the tumor was confined to the bronchus and lungs, and in 1 case the involvement was entirely confined to the bronchus and its corresponding lobe.

In the present series of cases, carcinoma was the only type of malignant growth found. Bronchial carcinoma was found in 96 per cent and alveolar carcinoma in 4 per cent. Of the bronchial carcinomas the small cell type predominated, occurring in 68 per cent.

CONCLUSIONS

Primary carcinoma of the lung is a comparatively frequent finding in the larger pathologic institutes. These tumors, in consideration of the time element from the first symptom to death, run a rapidly fatal course. The few patients with early suggestive pulmonary symptoms should be examined with great thoroughness, using all the available measures at one's disposal, to help in establishing an early diagnosis. By so doing, one may increase the percentage of diagnoses made while the tumor is confined to one lobe. In such a group lobectomy is indicated as a possible measure.

For the large percentage of cases in which operative intervention is not indicated, roentgen or radium therapy may considerably retard the growth and spread of the cancer and also help to alleviate disturbing symptoms caused by metastases.

Carcinoma of the lung should be classified with that of the mamma, thyroid, prostate and suprarenals as showing a very early tendency toward metastasis to bone.

STREPTOCOCCI IN THE BLOOD IN RHEUMATIC FEVER, RHEUMATOID ARTHRITIS AND OTHER DISEASES

BASED ON A STUDY OF 5,233 CONSECUTIVE BLOOD CULTURES

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AND

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A review of the literature dealing with the etiology of rheumatic fever shows clearly that much of the controversy in this important field is due to the paucity of adequate controls. It is a curious but undeniable fact that though bacteriologic investigations on this disease date back more than forty-five years, few of the numerous reports published are critical or well controlled. In order to establish a suitable background for the work to be reported in this paper, it may be well to mention briefly a number of the methods by which this problem has been attacked and to point out the doubtful justification in many instances for the conclusions drawn from the data obtained.

1 The description of organisms found post mortem and their acceptance as the etiologic agent of rheumatic fever. This error dates back to the work of Birch-Hirschfeld,¹ and was repeated by numerous investigators. In a study of the post-mortem bacteriologic changes in patients dying from diseases other than rheumatic fever, Epstein and Kugel² showed that streptococci can be recovered at autopsy in 40 per cent of cases from normal heart valves, in 47 per cent from the myocardium and in 79 per cent from the blood stream.

2 The alleged finding of specific streptococci in the throats of patients with rheumatic fever. Irvine-Jones³ showed that these organisms could not be distinguished culturally or immunologically from those found in normal throats. Hitchcock⁴ found streptococci almost as frequently in the throats of nonrheumatic as in those of rheumatic patients.

3 The significance given to the finding of minimal numbers of streptococci in the joints or subcutaneous nodules in cases of rheumatic fever. Shands⁵ has recently reported the finding of streptococci in 2 of 10 Charcot joints and in 1

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1 Birch-Hirschfeld. Wiesbaden Medical Congress, 1888, quoted by Thomson, D., and Thomson, R. *Annals of the Pickett-Thomson Research Laboratory* 4:1 (Nov., pt. 1) 1928.

2 Epstein, E. Z., and Kugel, M. A. *J. Infect. Dis.* 44:327, 1929.

3 Irvine-Jones, E. I. M. *Skin Sensitivity of Rheumatic Subjects to Streptococcus Filtrates*, *Arch. Int. Med.* 42:784 (Nov.) 1928.

4 Hitchcock, C. H. *J. Exper. Med.* 42:377, 1925.

5 Shands, A. R. *South. M. J.* 23:818, 1930.

gonorrheal arthritic joint (with gonococci) We have had similar experience with the latter condition Menkin⁶ has given experimental proof of the secondary localization of organisms in an inflamed site

4. The serologic behavior of streptococci Few efforts have been made to classify serologically the streptococci obtained in cases of rheumatic fever and rheumatoid arthritis In most instances agglutinin absorption was not attempted Recently, however, by the use of agglutination as well as agglutinin absorption methods, Cecil, Nicholls and Stainsby⁷ were able to group the *Streptococcus alpha* organisms obtained from the blood and joints of patients with rheumatic fever into 3 types and a fourth heterogeneous group It remains to be determined whether secondary invaders cannot be similarly grouped

5 The results obtained from the injection of vaccines and serum These results are still used as arguments to support the contention that a given organism is the etiologic agent of rheumatic fever The difficulty of differentiating specific from nonspecific effects, together with other obvious objections to the acceptance of this form of evidence, is too well known to require discussion

6 The results of skin tests Following Birkhaug's⁸ demonstration that persons who have suffered from rheumatic fever are more susceptible to intracutaneous injections of toxic filtrates from *Streptococcus gamma* than are other groups of persons, Swift, Derick and Hitchcock⁹ showed the same to be true for *Streptococcus alpha*, as well as nucleoproteins from various types of streptococci These authors also showed that patients suffering from other diseases displayed a similar skin sensitivity to these products

7 The confusion of bacterial endocarditis with verrucous endocarditis of the rheumatic type, or the tacit acceptance that one is a modification of the other This confusion has led to unjustified conclusions of experimental results

8 The experimental production of pathologic lesions (endocarditis, pericarditis, arthritis and myocarditis) in animals, with the assumption that this is evidence of the specificity of an organism with relation to the etiology of rheumatic fever Cole,¹⁰ Harris¹¹ and Horder¹² were the first to correct this error by showing that a variety of streptococci may produce these lesions when injected into animals Recently, similar efforts have been made with regard to subcutaneous nodules

9 The acceptance of certain forms of endocarditis and myocarditis produced in animals (particularly in rabbits) as the equivalent of rheumatic lesions in the human being This point has been critically examined and discussed by Thalhimer and Rothschild,¹³ Cecil,¹⁴ Swift¹⁵ and Gross, Loewe and Eliasoph,¹⁶ who showed that the lesions thus far produced experimentally cannot be so considered

6 Menkin, V J Exper Med 53 647, 1931

7 Cecil, R L, Nicholls, E E, and Stainsby, W J J Exper Med 50: 617, 1929, Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, Arch Int Med 43 571 (May) 1929, Am J M Sc 181 12, 1931

8 Birkhaug, K E Proc Soc Exper Biol & Med 24 541, 1927

9 Swift, H F, Derick, C L, and Hitchcock, C H. Tr A Am Physicians 43.192, 1928

10 Cole, R I J Infect Dis 1 714, 1904

11 Harris, N Tr Chicago Path Soc 6 303, 1905

12 Horder, T J Thirty-Sixth Annual Report of the Local Government Board, Report of the Medical Officer, 1906, p 279, Quart J Med 2 289, 1908

13 Thalhimer, W, and Rothschild, M A J Exper Med 19 429, 1914

14 Cecil, R L J Exper Med 24 739, 1916

15 Swift, H F Am J M Sc 170 631, 1925

16 Gross, Louis, Loewe, Leo, and Eliasoph, B J J Exper Med 50 41, 1929

10 Failure to recognize spontaneously occurring lesions in laboratory animals Miller¹⁷ was able to show that his control rabbits and guinea-pigs possessed myocardial lesions that he could not differentiate from those that he had attempted to reproduce experimentally

11 The significance attached to the finding during life of positive blood cultures, particularly of streptococci It is with this last point that this article is concerned Several excellent critical reports have been published on this aspect of the problem of rheumatic fever, among which may be mentioned those by Cole,¹⁰ Libman,¹⁸ Swift and Kinsella¹⁹ and Jordan²⁰ Many discrepancies exist as to the frequency with which various authors obtained positive blood cultures (streptococci) from cases of rheumatic fever, the optimum method to be used for this purpose and the type of streptococci recovered On the latter point, it may be mentioned that *Streptococcus alpha*, *beta* and *gamma* have been found

On the question of the percentage of positive blood cultures, figures vary from completely negative findings to such successful reports as those of Clawson,²¹ who isolated streptococci "in a relatively high percentage of cases," and those of Cecil, Nicholls and Stainsby,⁷ who obtained positive blood cultures in 26 of 31 cases (83.9 per cent) in their series of 1929 The latter investigators attributed their successes to the special technic used The value of the special technic has been questioned by Nye and Waelbaum²² and by Dawson, Olmstead and Boots,²³ who were unable to confirm the results obtained in cases of rheumatoid arthritis Incidentally, the criticisms that have thus far been made generally apply equally well to the reports on the bacterial etiology of rheumatoid arthritis

In examining the reports of those who obtained a relatively high incidence of streptococcemia in rheumatic fever and because of this are inclined to accept these organisms as the causative agent of the disease, it becomes apparent that in none of these studies were there employed as controls groups of diseases selected from as large a material as that from which the cases of rheumatic fever were drawn

The records in the Mount Sinai Hospital for the last four and a half years (ending Dec 30, 1930) show that blood cultures were taken in 188 cases of acute rheumatic fever with polyarthritis, in 126 cases of chronic rheumatic cardiovalvular disease with recurrences and in 49 cases of rheumatoid arthritis (for an explanation of the terms, see section on "Definitions," p 1082) A study of the incidence of strepto-

17 Miller, C P J Exper Med **40** 525 and 543, 1924

18 Libman, E Bull Johns Hopkins Hosp **17** 215, 1906, Characterization of Various Forms of Endocarditis, J A M A **80** 813 (March 24) 1923, New York Academy of Medicine Lectures on Medicine and Surgery, New York, Paul B Hoeber, Inc, 1927, vol 69

19 Swift, H F, and Kinsella, R A Bacteriologic Studies in Acute Rheumatic Fever, Arch Int Med **19** 381 (March) 1917

20 Jordan, E P The Microbic Etiology of Rheumatic Fever and Arthritis, Arch Path **10** 79 (July) 1930

21 Clawson, B J J Infect Dis **36** 444, 1925

22 Nye, R N, and Waelbaum, E A J Exper Med **52** 885, 1930

23 Dawson, M H, Olmstead, M, and Boots, R H Proc Soc Exper Biol & Med **28** 419, 1931

coccemia in these diseases can be of significance only if compared with other selected diseases or disease groups drawn from the total blood culture material from which the aforementioned groups were taken—in effect, from 5,233 cases. An investigation of this point was undertaken and forms the basis of this report. Furthermore, since it is the main purpose of this work to serve as an adequate control of the bacteriologic findings in the blood of patients suffering from rheumatic fever and rheumatoid arthritis and since alpha and gamma streptococci are the organisms most frequently found in these diseases, we chose our control groups with the following criteria in mind:

1 The diseases should not be obviously caused by a nonhemolytic streptococcus.

2 They should not be obviously associated with a massive blood invasion with nonhemolytic streptococci, such as occurs in subacute bacterial endocarditis.

3 The percentage incidence of the nonhemolytic streptococcemia should be within the same range as that found in rheumatic fever and rheumatoid arthritis.

MATERIAL

Our material consists of 5,233 consecutive blood cultures taken, during the latter half of 1926 and during the years 1927, 1928, 1929 and 1930, from 3,869 patients in whom the possibility of a blood invasion was considered. Positive bacteriologic findings were obtained in 762 subjects. During this entire period there was little change in the full time bacteriologic staff, the entire work having been carried on under the supervision of Dr. Gregory Schwartzman. After the elimination from the control groups of the diseases that did not fulfil the requirements mentioned, the disease groups on which special emphasis will be laid may be tabulated as follows:

<i>Rheumatic and Rheumatoid Group</i>		Cases
I	Acute rheumatic fever with polyarthritis *	188
II	Chronic rheumatic cardiovascular disease *	126
III	Rheumatoid arthritis *	49
<i>Control Group</i>		
IV	Aplastic anemia	13
V	Perniciou anemia	11
VI	Leukemia	29
VII	Colitis *	41
VIII	Meningococcus meningitis	54
IX	Pyelitis and pyelonephritis	72

* For an explanation of the terms, see "Definitions," p. 1082.

DEFINITIONS

The accepted diagnostic criteria of active rheumatic infection, including tachycardia, fever, sedimentation time, leukocytosis, electrocardiographic changes, etc., were used in selection of the rheumatic cases. In order to determine whether there was any difference, so far as the incidence of streptococcemia was concerned, between the very active, acute form with polyarthritis and the milder form with recurrent attacks in which the mechanical symptoms predominate (i.e., due to the valvular defects), the cases were divided into two groups: acute rheumatic fever with polyarthritis and chronic rheumatic cardiovalvular disease.

Acute Rheumatic Fever with Polyarthritis—This group comprises typical cases in which polyarthritis is the predominant symptom. Only cases in which there was fever, leukocytosis or both are included. One case of chorea is also included.

Chronic Rheumatic Cardiovalvular Disease—As stated, this group includes cases in which the valvular defects on a rheumatic basis predominate, with recent reinfection, but without polyarthritis. Cases of atherosclerotic heart disease complicated by febrile conditions were obviously excluded from this group.

Rheumatoid Arthritis—This comprises a group of patients suffering from acute, subacute or chronic so-called infectious monarticular or polyarticular arthritis of nonrheumatic origin, and corresponds to the "rheumatoid arthritis" group under the classification of the British Ministry of Health and adopted by the International League for the Control of Rheumatism. Cases of gonorrheal origin were excluded. All of the patients, with rare exceptions, had fever, leukocytosis or both. Some had involvement of single joints, others, of multiple joints.

Colitis—Under this term are included cases of acute and chronic ulcerative colitis. Cases of amebic and tuberculous colitis are excluded.

Streptococcemia—We use this term to denote the presence of streptococci in the blood during life, giving it the same generic meaning as "bacteremia" as defined by Libman¹⁸. The term in no way indicates whether the invasion is transient or an essential part of the disease process.

Nonhemolytic Streptococci—The Brown²⁴ classification of streptococci is used in this report. In the older literature no sharp differentiation was made between *Streptococcus alpha* and *gamma*. Furthermore, it is particularly these two types that occur most frequently in cases of rheumatic fever and rheumatoid arthritis, and they are the basis of

24 Brown, J. H. Monogr. Rockefeller Inst. Med. Research, 1919, no. 9.

most of the comment. For these reasons we shall refer to the organisms collectively as "nonhemolytic streptococci" in the sense used by Libman¹⁸

U Cocci—In a number of cases a gram-positive coccus was obtained on blood culture, which, however, failed to grow on aerobic subcultures, so that it could not be identified. The failure to grow may have been due to two reasons: prompt autolysis in the medium or unsuitable aerobic conditions (if they were anaerobes). In some instances, however, growth did not take place even under strict anaerobiosis. These unidentified organisms will be referred to as *U cocci*, and will be given consideration so as to present an unbiased statistical picture.

TECHNIC OF THE BLOOD CULTURE

The antecubital area is sterilized by tincture of iodine, which is removed with alcohol in from three to five minutes. At least 23 cc of blood is withdrawn from the median basilic vein, when special cultural methods are employed, 40 cc is withdrawn. The various mediums are inoculated immediately at the bedside, and plates are poured.

In taking routine blood cultures, the following equipment is used: glass Luer syringes, of 20 cc capacity, needles, sterilized by means of dry heat in a special copper container at 185 C for an hour and a half, 4 sterile petri dishes, 2 test tubes, each containing 1 cc of sterile ascitic fluid, 2 sterile, empty test tubes, 1 tube of plain agar, 1 flask of plain broth, 1 flask of 2 per cent dextrose broth, and 1 flask of tomato dextrose peptone broth. The preparation of the special mediums will be described in the next section. The last 6 mediums mentioned constitute our "*Routine*" mediums.

The agar tubes are previously melted and kept at 50 C. The patient's blood is then drawn and distributed as follows: 5 cc to each flask, 2 cc each to the plain agar, dextrose agar and liver hormone agar tubes. Before pouring the plates, the agar and blood are mixed by pouring back and forth into sterile tubes under strict sterile precautions. One tube of dextrose agar and another of liver hormone agar are enriched with ascitic fluid before the plates are poured. One tube of ascitic fluid mixed with 5 cc of dextrose broth serves as a control for the sterility of the ascitic fluid. Likewise, the individual mediums are controlled for absolute sterility. Within half an hour, all the mediums are incubated at 37.5 C. The plates are examined daily, and by means of a capillary pipet subcultures are made daily from the 3 flasks on dextrose broth and dextrose ascitic agar. This procedure is repeated for four days if the cultures are negative. All gram-positive, chain-forming diplococci that do not show definite zones of complete hemolysis around the colonies on the blood plates are typed for pneumococcus and tested for bile solubility.

CULTURE METHODS

The special cultural methods employed are the anaerobic, the special aerobic and the method of Cecil, Nicholls and Stainsby. The following anaerobic culture mediums were used: the Smith-Noguchi rabbit kidney ascitic fluid, the Rosenow calf brain and cooked liver. The formulas for these mediums will be given. Two cubic centimeters of the patient's blood is added to each of the mediums in tubes, which are sealed with melted petrolatum. After incubation at 37.5 C for three days, the

tubes are opened, the films are stained, and the inoculum is transferred from each tube to cooked liver. All the tubes are then sealed and incubated for three days more. They are then opened and examined for growth. If negative, they are sealed and incubated for two weeks more, when a final examination and report are made.

Special Aerobic Method—This method was carried out as follows: from 10 to 12 cc of the patient's whole blood was inoculated into a 500 cc Erlenmeyer flask containing 100 cc of 0.4 per cent dextrose broth (p_H 7.4). Daily subcultures were made for a week. The features of the method are the large amount of blood used and the large surface of medium exposed to air.

Cecil Procedure—This procedure was carried out in detail as originally described. Twenty cubic centimeters or more of blood is taken from a vein of the arm. The blood is divided between two centrifuge tubes, allowed to clot and stored in the ice chest over night. The following morning the clots are loosened with a glass rod, and the tubes are placed in the centrifuge. After centrifugation, the serum is carefully removed with a pipet, and the clots are broken up with glass tubes one-fourth of an inch (0.64 cm) in diameter, drawn up in the tubes and transferred to two 3 ounce (11.25 cc) bottles, each containing 50 cc of beef heart infusion broth. The bottles are covered with paper caps and incubated at 37 C for one month. During this period the bottles are opened at five day intervals and subcultures are made on both blood agar-poured plates and blood broth tubes, 0.1 cc of the original broth culture being used in each case. If no growth is found at the end of a month, the original contents of the broth bottles are centrifuged and the sediment is cultured in fresh blood broth. Subcultures are made from the sediment on blood agar plates several days later, and if no organisms are found, the cultures are considered negative. Parallel control cultures are made of the rabbit's blood for a period corresponding to that during which the patient's blood is studied. The rabbit's blood is transferred to dextrose broth every five days, and films of the sediment are stained.

PREPARATION OF MEDIUMS

Plain Broth—To 500 Gm of chopped meat (beef or veal) is added 1,000 cc of tap water. The mixture is brought to the boiling point over an open flame and cooked slowly for fifteen minutes, it is then filtered through absorbent cotton and readjusted to the amount of 1,000 cc. To this infusion is added 10 Gm of Witte's peptone and 4 Gm of sodium phosphate. The p_H is adjusted to 7.8. The mixture is autoclaved for twenty minutes at 15 pounds of pressure, and the reaction is readjusted to a final p_H of 7.4 or 7.6.

Liver Hormone Broth and Agar—To 500 Gm of chopped veal or beef liver freed from fat are added 1,000 cc of water, 10 Gm of peptone, 4 Gm of anhydrous sodium phosphate, 10 Gm of dextrose the beaten whites of 2 eggs and 20 Gm of agar (if used for agar). All the ingredients are placed in the same receptacle and heated over a free flame up to 70 C, when the meat turns brown. Twenty-five cubic centimeters of sodium hydroxide is then added. Sterilization is carried out in the Arnold sterilizer for two hours. At the end of this time a firm clot is formed and the broth or agar can be decanted or siphoned off. The preparation is not filtered at any stage. The reaction is adjusted to p_H 7.6. The medium is autoclaved in flasks for twenty minutes at 15 pounds of pressure. After transfer to tubes it is again autoclaved for fifteen minutes and 15 pounds of pressure.

Tomato-Dextrose-Peptide Broth (Shwartzman)—Tomatoes are washed in warm water and gently dried with a towel. Small pieces are cut and boiled for fifteen minutes over an open flame. The preparation is filtered first through gauze and then through absorbent cotton. The extract is stored in the ice chest over night. The next day it is filtered by means of suction through several layers of paper in a Buchner funnel. After this the fluid is clear enough to be filtered through Berkefeld filters, candle V being used first and then candle N. No further sterilization is necessary. The fluid is stored in the ice chest until needed. Before use the reaction is adjusted by means of sterile sodium hydroxide, which is added to the extract until the color changes to a light brown. This indicates a p_H of about 7.6. To 90 cc of 2 per cent peptone and 1 per cent dextrose broth is added 10 cc of sterile tomato extract. The mixture is then sterilized in the Arnold sterilizer for ten minutes. The medium thus prepared rarely proves to be contaminated.

Cooked Liver—To 1,000 cc of 1 per cent dextrose broth is added 1 pound (453.6 Gm) of beef liver. The mixture is boiled over an open flame for fifteen minutes. The reaction is adjusted to p_H 7.6. The liver is cut into small cubes and placed in tall tubes used for the Smith-Noguchi medium and autoclaved for twenty minutes at 15 pounds of pressure.

Rosenow Calf-Brain Medium—A small piece of white marble is introduced into a tube, then a cube of raw calf brain and 10 cc of plain broth. The p_H is adjusted to 7.4. The mixture is autoclaved for thirty minutes at fifteen pounds of pressure.

Cecil, Nichols and Stansby's Beef Heart Infusion Broth—This medium was carefully prepared and adjusted as described in the original work. The blood agar plates were made as follows: eight cubic centimeters of agar (1.5 per cent beef heart infusion) is melted and cooled to 50 C. To this are added 0.5 cc of whole rabbit blood and 0.1 cc of the original broth culture, and the plate is poured.

BACTERIOLOGIC RESULTS OF BLOOD CULTURES

I *Acute Rheumatic Fever with Polyarthrits*—One hundred and eighty-eight cases are included in this group. While cultures were taken in many cases in which salicylates were not administered, no especial control of this factor was made. With a single exception, all the patients were febrile or had leukocytosis at the time the blood was examined.

Negative Results. In this series, 168 cases proved sterile. Of these cases, 13 were fatal. Twenty-three cases of this negative group were cultured on two occasions, 4 on three occasions, 1 on five occasions, and 1 nine times. One hundred and fifty-eight of these cases were studied with routine methods only. In addition to the routine mediums, however, 77 cases were studied by the special aerobic method, 10 by the Cecil and 65 with the aid of the anaerobic Smith-Noguchi, Rosenow, or cooked liver mediums.

Positive Results. Positive bacteriologic findings were obtained in 20 cases. In 5 cases the cultures were repeated. Gram-positive cocci were obtained in 2 of the repeated cultures. There was only 1 fatal case in this series. In 3 of 20 instances in which gram-positive cocci were obtained it was impossible to obtain growth on subculture. Of the 17 that grew on subculture, 1 was *Streptococcus beta*, 1 pneumococcus type II, 4 *Streptococcus alpha* and 11 *Streptococcus gamma* (8 per cent nonhemolytic streptococci). *B. coli* was obtained in 1 of the cases in which the gram-positive organism did not grow on subculture.

In 10 of the positive cases, routine mediums only were employed. In the other 10, special mediums were used in addition. Twelve cultures were made. In only 1 of the latter group did an organism appear (*Streptococcus alpha*) on the special mediums alone (special aerobic). On the other hand, whereas organisms grew in 9 of these 12 cultures in the routine mediums, growth was obtained in only 4 in the special mediums.

Considering the group as a whole, of the 178 cases studied by the routine methods, positive results were obtained in 19 (11 per cent). Of the 86 cases studied by the special aerobic method, 3 were positive (3.5 per cent). The organisms were all *Streptococcus alpha*. Of the 11 cases studied by the Cecil method, none was positive. The 67 anaerobic cultures were all negative. The question of the relative value of different mediums will be discussed later.

II *Chronic Rheumatic Cardiovalvular Disease*—This group comprises 126 cases, in practically all of which there was fever or leukocytosis, or both.

Negative Results. The blood cultures in 119 cases of the series yielded negative results. Fifteen of the cases were fatal. In 5 of the negative cases the blood was cultured twice, in 2, 3 times, and in 1,

4 times Thirty-six cases were studied by the special aerobic technic None of these cases was studied by the Cecil method Forty-six cases were studied anaerobically with the Smith-Noguchi, Rosenow and cooked liver mediums

Positive Results Seven of the cases in this group yielded gram-positive cocci on blood culture In a single case the organism failed to grow on subculture In addition to the unidentified coccus an unidentified bacillus that failed to grow on subculture was obtained on anaerobic mediums Of the remaining 6 cases, 3 showed *Streptococcus alpha* and 3 *Streptococcus gamma* (5 per cent nonhemolytic streptococci) Three of these cases were fatal Two of the 7 cases were studied by the special aerobic technic, none by the Cecil method and 4 by anaerobic methods

In the 5 cases in which routine as well as special mediums were used, 7 cultures were taken Organisms were obtained in the routine mediums in 5 cultures and in the special mediums in 3 In 1 of these, growth was obtained in the special aerobic flask only—not in the routine mediums

Considering the group as a whole, of the 125 cases studied by the routine methods, positive results were obtained in 5 (4 per cent nonhemolytic streptococci) Of the 38 cases studied by the special aerobic method, 2 were positive, 1 yielded *Streptococcus alpha* and 1 streptococcus gamma (5 per cent nonhemolytic streptococci) The Cecil method was not used in this group The 50 anaerobic cultures were negative

III Rheumatoid Arthritis—Forty-eight cases of acute, subacute and chronic infectious arthritis were studied There were no fatalities in this series

Negative Results In 44 cases the blood cultures were negative In 9 of these, the cultures were repeated Eighteen cases were studied by the special aerobic technic, in 1 case 3 times and in another twice In 5 cases the cultures were taken according to the Cecil procedure, and in 7 cases, anaerobically

Positive Results Four cases yielded gram-positive cocci in the blood cultures In 2 of these, the organism failed to grow on subculture On repetition in one of the cases, a hemolytic streptococcus and *Staphylococcus albus* were obtained In the remaining 2 cases, *Streptococcus gamma* grew (4 per cent nonhemolytic streptococci)

In 4 positive cases, 8 cultures were taken In all of these, routine mediums were used In addition, special mediums were used in 6 of the cultures Organisms grew in the routine mediums in 3 cultures and in the special mediums in 2 In a single case growth was obtained on the special mediums only (special aerobic and Rosenow's)

Considering the group as a whole, of the 44 cases studied by routine methods, positive results were obtained in 4 (9 per cent) Two of these showed nonhemolytic streptococci (4.5 per cent) Of the 21 cases

studied by the special aerobic method, 1 was positive and showed *Streptococcus gamma* (5 per cent). Five Cecil cultures were negative. Ten cases studied with anaerobic methods gave 2 positive results: 1 *Streptococcus gamma* (10 per cent), and 1 an unidentified gram-positive coccus that failed to grow on subculture.

Of the 3,869 cases in which blood cultures were taken, 363 comprise the 3 groups just considered and 144 were cases of subacute bacterial endocarditis in which a streptococcemia is to be expected in a large proportion of cases. If we eliminate the total of these 2, 3,362 cases are left, in which nonhemolytic streptococci and U cocci were found in 51 (1.5 per cent) and nonhemolytic streptococci in 43 (1.3 per cent).

The accompanying table lists all cases in which nonhemolytic streptococci and U cocci were found in the blood of the control series, and also data on the mediums used, the temperature of the patient at the time the cultures were taken, the white blood cell count and the final diagnosis. Whereas no indication is given in the table of the total number of cases making up the different diseases studied, it may be said at once that with the exception of the conditions listed as "control groups" the incidence of nonhemolytic streptococcemia in any given group was under 1.5 per cent. Routine mediums were employed in all the positive cases. In addition, in 17 cases the special aerobic method was added, in 2 cases, the Cecil method, and in 12 cases, anaerobic method.

IV *Aplastic Anemia*—There were 13 cases in this group, with 2 positive results (15.5 per cent), in 1, *Streptococcus alpha*, in the other, *Streptococcus gamma* (see table, cases 1 and 2). A single anaerobic culture was employed, with negative results. The positive results were obtained on routine mediums. Both cases terminated fatally.

V *Perniciou Anemia*—There were 11 cases in this group, with 1 positive result (*Streptococcus alpha*), which was obtained in routine mediums (9 per cent). This case was fatal (see table, case 5).

VI *Leukemia*—There were 29 cases in this group. In 2, *Streptococcus gamma* was obtained in the routine mediums (7 per cent). The cases were fatal (see table, cases 3 and 4).

VII *Colitis*—There were 41 cases in this group, with 4 positive results (10 per cent) (see table, cases 7 to 10). Routine mediums only were used in the 5 cultures taken. *Streptococcus gamma* (identified as *Enterococcus* by esculin fermentation test, etc.) was obtained in 1 case, and in another *Streptococcus alpha* was obtained on solid mediums (5 per cent nonhemolytic streptococci). In 2 cases U cocci were found, and in 1, *Staphylococcus albus*. The latter case was the only one in which the patient survived.

Cases of Nonheumatic-Rheumatoid Disease with Nonhemolytic Streptococci or

U Cocci in the Blood

Case	Blood Culture No	Mediums	Temperature, F	White Blood Cells	Bacteriologic Findings	Clinical Result and Diagnosis
1	13714 13743	R R	103 0 103 6	1,200 1,200	SG 2, tomato extract U 2, plain broth	Died, aplastic anemia
2	15223	R, Nog	104 6	1,200	SA 2, tomato extract	Died, aplastic anemia
3	14168	R	103 0	18,600	SG 3, plain bouillon	Died, acute myeloblastic leukemia
4	15551	R	102 6		SG 2, 5, dextrose and peptone flasks	Died, acute leukopenic myeloid leukemia
5	17950	R	103 8	18,200	SA 2, dextrose and tomato extract	Died, pernicious anemia bronchopneumonia
6	14110	R	105 0		U 3, fluid mediums	Well, cervical adenitis (incision and drainage)
7	14801	R	101 0	10,450	SG 2 enterococcus in dextrose and peptone flasks	Died, chronic ulcerative colitis
8	16089	R	104 0	6,400	U 2, dextrose flask	Died chronic ulcerative colitis, tonsillitis
9	17607 17612	R R	101 8 103 2	13,300 7,800	S 4, dextrose and tomato extract U 4, plain bouillon	Died, chronic ulcerative colitis
10	16822	R	104 0		SA-3, dextrose bouillon, and 1 colony on dextrose serum agar	Well, acute colitis complicating prostatectomy
11	14969	R	100 6		SA 1, all mediums, colonies too numerous to count	Died, meningitis, Streptococcus viridans, necropsy
12	15142	R, Ros, Liv		8,800	U 2, tomato extract	Died, meningitis tuberculous?
13	15477	R	104 2	11,400	SA 1 60 colonies per cubic centimeter of blood	Well meningococcus meningitis
14	15649	R	103 0		SG 4, fluid mediums	Well, meningococcus meningitis
15	13447	R	104 0	47,000	SG 1, 2 colonies per cubic centimeter of blood	Died, lung neoplasm, hemothorax
16	14010	R R	105 8	26,000	SA 2, all fluid mediums	Well, lobar pneumonia
17	14206	R	105 0	15,500	SG 4, plain and dextrose flasks not bile soluble, did not grow in mouse	Well, bronchopneumonia
18	14213	R	103 6	25,800	SA 4, plain and dextrose flasks, not a pneumococcus	Well, bronchopneumonia
19	15612	R	103 0	13,300	SA 4, 2 colonies per cubic centimeter of blood on 1 plate only	Well, lobar pneumonia
20	17469	R	102 0	8,200	SA 1, tomato extract	Well, lobar pneumonia
21	17637	R	103 0	25,000	SA 2, tomato extract	Well, pleuropneumonia
22	14843	R	101 9		U 2, dextrose and tomato extract	Well, grip
23	17850	R	100 6	19,200	SA 4, dextrose broth only	Well, pychitis
24	14683	R	103 4	12,750	SA 4, peptone flask	Well, pyelitis
25	14718	R	103 6		SA 4, peptone and tomato extract	Well, pyelitis
26	16095	R	106 0		SA 4, 1 flask	Improved, pyelo nephritis
27	14492	R, Liv, Ros, Nog	102 6		SA 2 plain broth flask	Improved, glomerulo nephritis, benign hemorrhagia

* Explanation of abbreviations and numerals R indicates routine culture medium Ce, Cecil technic Ros, Rosenow's medium, Liv, cooked liver anaerobic medium, Nog, Smith Noguchi medium SA, Streptococcus alpha (viridans), SG, Streptococcus gamma (nonhemolytic), S, Staphylococcus albus, U, unidentified gram positive cocci in short or long chains which failed to grow in subculture The numerals represent the day of subculture

Cases of Nonheumatic-Rheumatoid Disease with Nonhemolytic Streptococci or U Cocci in the Blood—Continued*

Case	Blood Culture No	Mediums	Temperature, F	White Blood Cells	Bacteriologic Findings	Clinical Result and Diagnosis
28	15022	R	99.2		SG 2, plain broth only	Well, pyelonephritis adenoma of prostate (prostatectomy)
29	14907	R	105.2	12,000	U 2, 1 flask	Improved, erysipelas of face, pansinusitis
30	17553	R	105.0	20,000	SG 2, dextrose flask	Well, erysipelas, abscess of foot
31	18785	R	102.6	21,250	SG 1, all mediums 2 colonies per cubic centimeter	Died, erysipelas of biopsy wound lymphosarcoma
32	15068	R	103.4	25,000	SA 4, fluid medium	Well, acute mastoiditis
33	14934	R, Ros, Liv	101.4	20,000	SG-4, anaerobic medium only	Died, sinus thrombosis acute mastoiditis
	15006	R, Ros, Liv			SG 3, tomato extract aerobic	
34	14025	R	103.8		SA 2, tomato extract and dextrose serum medium, 2 colonies per cubic centimeter of blood	Died, sinus thrombosis acute mastoiditis
35	14905	R	102.0	16,000	U 4, tomato extract	Improved abscess of thigh and penis
36	17856	R	103.8		SA 1, dextrose flask	Well, phlegmon of chest wall, incision and drainage
37	13582	R	104.0		SA 2, dextrose flask	Well, abscess of thigh
38	18206	R	102.8	4,800	SA 2, tomato extract	Died, parotid abscess
39	13635	R	99.0		SA 2, flasks	Died, parotid abscess
40	15245	R, Ros, Nog	105.0	9,000	SA 4, aerobic	Died, postpartum sepsis
	15261	R, Liv	104.8		SA 2, aerobic and an aerobic fluid medium	
	15265	R, Liv, Ros	105.5	14,000	SA 3 aerobic and an aerobic fluid medium	
41	13995	R	105.0		SG 2, dextrose broth, no plates made	Died, streptococcus sepsis
42	15027	R	104.0	11,300	SA 2, all mediums	Died, streptococcus sepsis, peritonitis
43	17892	R	101.0	8,600	Several greenish colonies on dextrose agar plates, failed to grow on transplant	Well, typhoid fever
44	13742	R	101.6	10,600	U 2, flasks	Well, periostitis
45	17126	R, Liv	99.0		SA 4 anaerobic medium	Improved, osteomyelitis of clavicle and femur, incision and drainage
46	16653	R			SG 2, flasks only, in transplant growing on anaerobic plates	Improved, sacroiliac arthritis
47	16722	R, Liv, Ros	102.2		SG 4, 1 flask	Died, carcinoma of ascending colon fecal fistula
48	15122	R, Nog	104.0		SA 2, dextrose and tomato extract flasks	Died, stenosis of common bile duct, liver abscess
	15160	R, Liv, Nog	103.8	17,600	SA 2, fluid aerobic and anaerobic medium	
49	17335	R	101.8		SA 4, dextrose flask	Improved gonorrheal salpingitis, arthritis of right knee
	17390	R, Ce	101.0		SA 3, all routine flasks	
50	13877	R	99.6		SG 2	Well, erythema multiforme
51	14837	R, Ros, Liv, Nog			SA 2, aerobic, dextrose flask	Well right inguinal hernia chronic appendicitis hernioplasty

VIII *Menngococcus Menngitis*—There were 54 cases in this group, with 2 positive results (4 per cent) on routine mediums (see table, cases 13 and 14) In 1 case *Streptococcus alpha* was obtained (60 colonies per cubic centimeter), in another case, *Streptococcus gamma* The patients in both cases recovered

IX *Pyelitis and Pyelonephritis*—There were 72 cases in this group, with 5 positive results (7 per cent), as shown in the table (cases 23, 24, 25, 26 and 28) Routine mediums were employed in all cases *Streptococcus alpha* was obtained 4 times, *Streptococcus gamma*, once All of the patients recovered In 1 case the urine was not cultured In 1 case the culture of the urine was negative, in 3 cases, it contained *B coli*

COMMENT

Before proceeding with the comment, one must bear clearly in mind the fact that to all intents and purposes there exist 2 types of streptococcemia One is associated with a massive blood invasion such, for example, as occurs in subacute bacterial endocarditis In these cases numerous colonies are found in solid as well as in fluid mediums On the other hand, in the individual diseases forming the 9 groups referred to, the streptococcemia is minimal and irregular Very often repeated cultures fail to confirm the finding of organisms, and when they do grow they appear on solid mediums with extreme rarity Libman¹⁸ has called attention to this fact, and he has shown that this is a means of differentiating for practical purposes between the positive cultures obtained in cases of subacute bacterial endocarditis and those obtained in cases of rheumatic fever For the sake of discussion, then, we may say that the 9 diseases considered in this article are associated with a "transitory bacteremia" or a "transitory streptococcemia"

In an attempt to arrive at the possible significance of these "transitory streptococcemias," especially those found in our control cases, several important points must be considered These may be stated in the form of the following questions

- 1 Are our control groups adequate?
- 2 Do these bacterial invasions occur shortly before death, i e., are they agonal?
- 3 Was the patient's illness caused by the streptococcus recovered from the blood stream?
- 4 Were our methods of blood culture adequate?
- 5 What is the relative value of the culture methods used?

In order to answer the first question, it is advisable to compare our control group with the diseases making up the rheumatic-rheumatoid group The group of 188 cases of acute rheumatic fever with polyarthritis had an 8 per cent incidence of nonhemolytic streptococcemia (4 cases *Streptococcus alpha*, 11 cases *Streptococcus gamma*), the

group of 126 cases of chronic rheumatic cardioalvular disease had a 5 per cent incidence of nonhemolytic streptococcemia (3 cases *Streptococcus alpha*, 3 cases *Streptococcus gamma*), and the group of 48 cases of rheumatoid arthritis had a 4 per cent incidence of nonhemolytic streptococcemia (*Streptococcus gamma*). Taken together, these selected groups form a total of 363 cases with an incidence in nonhemolytic streptococcemia of 6 + per cent.

Compared to this our control groups are, on the whole, smaller (obviously due to the fact that these diseases were not especially studied for bacteremia), yet taken together they number 220 cases, in 8 of which *Streptococcus alpha* was recovered from the blood and in 6, *Streptococcus gamma* (the U cocci are not considered). This totals 14 cases with an incidence of nonhemolytic streptococcemia of 6 + per cent, which is the figure obtained for the rheumatic-rheumatoid group. Furthermore, with the exception of a single small group (aplastic anemia), the individual control groups show an incidence of nonhemolytic streptococcemia that runs fairly consistently around the 6 per cent mark. Since we are not interested in the individual control groups for the diseases per se, and, furthermore, since there are no very wide differences between them in the incidence of nonhemolytic streptococcemia, it seems to us to be permissible to add them together for control purposes. We therefore feel that our collective control material of 220 cases is adequate.

The mortality rates in the control groups (100, 100, 100, 100, 0 and 0 per cent, respectively) by their very nature must necessarily be high. This, however, by no means invalidates the findings, because in no instance was the blood culture taken less than ten days before death. Usually it was taken several weeks before death. Obviously, therefore, the patients were not moribund at the time. Then, too, more than half of the total control material (groups VIII and IX) was associated with no fatality, yet the incidence of nonhemolytic streptococcemia is about the same as in the rest of the groups.

In considering the possible relationship between the organisms found on blood culture and the diseases constituting the control groups, it is obvious that aplastic anemia, pernicious anemia, leukemia and meningococcus meningitis may be immediately dismissed from consideration on this account. Cultures of the urine in the cases of pyelitis and pyelonephritis did not implicate the nonhemolytic streptococci as responsible for the disease. There remains the colitis group, which must be considered mainly because of Bargaen's²⁵ claims that a streptococcus is the etiologic agent in this disease. However, as will be noted, in the 2 posi-

²⁵ Bargaen, J. A. Chronic Ulcerative Colitis, *Arch Int Med* **45** 559 (April) 1930.

tive cases different organisms were obtained by us (*Streptococcus alpha* and *Streptococcus gamma*) Furthermore, Crohn and Shwartzman²⁶ reported on the same cases, and, while not denying the possibility that these organisms may play an etiologic rôle in the disease itself, gave ample reasons for believing that they are probably secondary invaders

The adequacy of our methods was shown in several ways First, positive cultures were obtained in a high percentage by our methods from cases obviously associated with streptococcemia Thus, during the entire period of five years covered by this study, 23 cases of subacute streptococcus endocarditis in the active stages (i e, bacteria in the vegetation crushings) came to autopsy, and in 21 of these (95.5 per cent) the organisms were easily cultivated from the blood Furthermore, the average percentage of positive cultures in the cases in the hospital on the whole presents a remarkable constancy year in and out, showing that there is no appreciable variation in the sensitiveness of the mediums or any peaks of unusually high incidence in positive cultures

Apart from this—and this brings us to the fifth question—our routine mediums acquitted themselves better than the special mediums employed Thus, taking all the cases comprising the rheumatic-rheumatoid group, nonhemolytic streptococci grew 27 times in 347 cultures when routine mediums were employed (8 per cent), 6 times in 145 cultures by the special aerobic method (4 per cent), once in 127 cultures by anaerobic methods (—1 per cent) and not at all in the 16 Cecil cultures As was pointed out, on a few occasions streptococci grew by the special aerobic method alone For this reason, this method may be considered a useful addition to blood culture technic In a very limited experience, the Cecil methods proved inferior to the routine method in our hands

It is held by many that rheumatic fever and rheumatoid arthritis are associated with a consistent streptococcemia, that with special methods the incidence of positive blood cultures is quite high, and that while streptococci may occur as transient invaders in other diseases, such an occurrence is quite rare The facts presented in the article, however, are at variance with these views

SUMMARY

In summarizing the facts presented, we may say that of 5,233 consecutive blood cultures taken during five consecutive years under practically the same conditions, positive bacteriologic findings were obtained in 762 subjects On analyzing chiefly the incidence of streptococcemia of the alpha and gamma types in 9 diseases other than those associated with a massive streptococcemia (e g, subacute bacterial

²⁶ Crohn, B B, and Shwartzman, G J Lab & Clin Med 14 722, 1929

endocarditis), it is found that acute rheumatic fever with polyarthritis forms a group of 188 cases with a nonhemolytic streptococcemia of 8 per cent, chronic rheumatic cardiovalvular disease forms a group of 126 cases with a nonhemolytic streptococcemia of 5 per cent, rheumatoid arthritis forms a group of 48 cases with a nonhemolytic streptococcemia of 4 per cent, aplastic anemia forms a group of 13 cases with a nonhemolytic streptococcemia of 15.5 per cent, pernicious anemia forms a group of 11 cases with a nonhemolytic streptococcemia of 5 per cent, meningococcus meningitis forms a group of 54 cases with a nonhemolytic streptococcemia of 4 per cent, and pyelitis and pyelonephritis form a group of 72 cases with a nonhemolytic streptococcemia of 7 per cent.

The first 3 diseases mentioned (the rheumatic-rheumatoid group) form a group of 363 cases, with an incidence of nonhemolytic streptococcemia of 6 + per cent. The last 6 diseases mentioned (control) form a group of 220 cases, with an incidence of nonhemolytic streptococcemia of 6 + per cent.

These studies also show that the bacterial invasions are not agonal, and that they are not the primary cause of the diseases comprising the control group. Furthermore, it is to be noted that the methods employed were adequate, and that, in our hands, our routine methods were at least as sensitive as the special aerobic, Smith-Noguchi, Rosenow and Cecil methods. Our experience with the last named method, however, is limited.

CONCLUSIONS

Study of 5,233 consecutive blood cultures in a general hospital shows that with adequately sensitive methods an incidence of nonhemolytic streptococcemia (alpha and gamma types) between 4 and 15.5 per cent with an average of 6 + per cent occurs in at least 9 diseases, i. e., acute rheumatic fever with polyarthritis, chronic rheumatic cardiovalvular disease, rheumatoid arthritis, aplastic anemia, pernicious anemia, leukemia, colitis, meningococcus meningitis and pyelitis and pyelonephritis. On the basis of the incidence of the "transient" streptococcemia alone, these organisms cannot justifiably be considered as the causative agents of these diseases.

Book Reviews

Pediatric Education Report of the Subcommittee on Medical Education
White House Conference on Child Health and Protection Borden S Veeder,
Chairman Section on Medical Service Committee on Medical Care for
Children Paper Pp 109 New York Century Company, 1931

"All our knowledge of the preservation of the health of the child, the prevention of disease, and the care of the sick or abnormal child comes directly from the medical sciences In organized health work which has so largely occupied the time of the White House Conference on Child Health and Protection we are apt to forget that the vast majority of American children today are dependent on the interest and care of a private physician for their physical well-being and health, and not upon an organization"

With these ideas in view, the subcommittee on medical education undertook a study of medical education so far as it related to the teaching of pediatrics in the medical schools, and to pediatric practice as current in the medical profession today The committee sent questionnaires to pediatricians, physicians especially interested in pediatrics and general practitioners There were 3,569 questionnaires sent, and 2,374, or 67 per cent, replies were received

Of those practicing pediatrics wholly or mainly, 44 per cent felt that their course pertaining to the normal child and his health was mediocre or unsatisfactory in view of their present experience "Further, the number who regarded the course as very satisfactory increases steadily the more recent the graduate" "Lack of clinical experience" is the most commonly mentioned deficiency "Neglect of consideration of the normal child" is second, and "too little time given to pediatrics" is third

More than two thirds of the men in general practice for ten or fifteen years feel that their course in pediatrics was satisfactory Instruction as a whole in "contagious diseases" seems to have been most satisfactory, and that in "preventive measures" and "new-born" comes second The most unsatisfactory course appears to have been that in "minor ailments"

Medical schools show the greatest variations in the size of the student body and faculty, yet all cover the same work in the same time There is the greatest difference in arrangement of curriculums and methods of presentation It was found that 35 per cent of the medical schools studied had insufficient hours to teach pediatrics properly, this deduction being made from the amount of time most schools find it necessary or desirable to assign to the subject Only half of them use the well-baby clinic as a teaching facility Over half of the schools reporting on their teaching on the newly born give less than ten hours' instruction In quite a large number of the schools the facilities for bed-side teaching of communicable diseases in childhood are quite inadequate As a whole, most of the medical schools today have adequate teaching facilities in the form of available hospital beds for the pediatric department, but in a few schools the teaching facilities are obviously inadequate

Postgraduate work is being given by two methods (1) intensive courses of review given in hospitals and medical centers during certain periods of the year, (2) extension courses given by visiting instructors in communities Of physicians listed as specialists, 67 per cent had taken postgraduate instruction Interest in postgraduate work was not confined to certain localities, but was well distributed over the country The indication was that if proper courses were offered there would be no lack of physicians who would take advantage of them

The conclusions that the subcommittee reached were 1 Pediatrics should be recognized as a fundamental branch of clinical medicine and should be organized as an independent department of medical schools 2 Adequate teaching staff,

hospital and clinical facilities and laboratories should be provided 3 Special stress should be laid on the teaching of growth and development of normal children of all ages, individual and social preventive medicine, diseases of childhood and nutrition 4 The minimum time devoted to pediatrics by the undergraduate student should be two hundred hours, with possible additional electives 5 Correct pediatric pedagogy should be studied and intensive review and extension courses provided for postgraduate study

The reading of the details of the report will be a great benefit to any one interested in the progress of pediatrics

Imhotep to Harvey Backgrounds of Medical History By C N B Camac
With a foreword by Henry Fairfield Osborn Price, \$3.75 Pp 324 New York Paul B Hoeber, Inc, 1931

Camac, in this book (Imhotep representing early Egypt, about 3000 B C, and Harvey representing the seventeenth century), has presented a general survey of medical history covering a period of, roughly, four thousand, five hundred years The rise of medical science is shown in relation to learning in general, other sciences and philosophy One might say that intellectual development (used in the broad sense) throughout this time is the fabric of the book, while medicine appears as the most conspicuous thread This thread sometimes becomes so thin as almost to disappear, but when this occurs the fabric itself appears defective and all learning is at low ebb The most conspicuous flaw is, of course the Middle Ages

The construction of the book deserves comment The author devotes a chapter (sometimes two) to each broad division in the history of science, e g, pre-Greek science, Greek and Roman medicine, the Middle Ages—a period of the retrogression of science, the pre-Renaissance, the Renaissance and the seventeenth century In addition, where it seemed necessary in order to effect a more thorough understanding, the author has inserted chapters dealing exclusively with the environment in which the scientist worked There is also a chapter entitled "Schools of Thought in Medicine," and one containing historic records and quotations from various sources—some referring specifically to medicine, others not He concludes the book with a bibliography of some length One wishes that he might also have included an index At the beginning of the chapters dealing with certain periods is a page or two containing information about those years in tabulated form For example, in the chapter on Greek and Roman medicine the author includes in the summary pages a list of the pursuits of that time, the elements on which medical practices were based, the important records and the names and dates of the important writers and teachers This device aided in unifying the period and helped to keep it clearly in mind It was fitting to have the forward written by so fine a student of "origins" as Henry Fairfield Osborn

The purpose of the book, as the author states at the outset, is to furnish a "background" of medical history, "he has drawn the picture in large strokes, leaving to the reader the filling in of detail which can be obtained from biographies and specialized works" The author goes far toward aiding the reader to fill in the details by his many references to representative and standard works He hopes that by noting the reception accorded to the discoveries of the past, we may learn how to accept the achievements of our own time and avoid "disputes and dissensions, which discredit science" The environment in which the scientist labored throughout this long time is graphically depicted, so that one appreciates what was accomplished and understands why more could not have taken place

This book should prove valuable and interesting to the medical profession (1) to those especially interested in science who "may find here lessons applicable to our own times," (2) to those engaged in teaching who will find descriptions of teaching institutions and methods, (3) to those who have a natural love of history and are desirous of learning all they can about the evolution of their profession, (4) to those who desire a handbook of medical history for reference to general

problems. The layman who has acquired an interest in medicine will find the book to his liking, as it is written in a manner that he can understand. In general, it is an excellent introduction to larger and more comprehensive books devoted to the history of medicine.

The book is written in a clear, interesting manner which is neither too detailed nor too abstract. The value of any such work lies in the author's ability to discriminate between the significant and the unimportant matters. The author of this book showed evidence of sound judgment in this respect. Furthermore, his study of various aspects of the periods he touches, say, the political, the religious and the cultural, has enabled him to draw a more complete and unified picture than he could otherwise have done.

Nucleic Acids By P. A. Levene, The Rockefeller Institute for Medical Research, and Lawrence W. Bass, Assistant Director of Research, The Borden Company. American Chemical Society Monograph Series, no. 56. Cloth. Price, \$4.50. Pp. 337. New York: The Chemical Catalog Company Inc., 1931.

The subject matter in this monograph is presented in an entertaining, systematic and accurate style and from the historical point of view, because as the authors state in their preface, the progress in our knowledge on nucleic acids is largely through "paths of error and controversy" and "it would be an injustice to many if the monograph contained only the views that seem correct today." All the essential details on the chemistry of carbohydrates, imidazole, pyrimidine bases, purine bases and so on through the more complex units to the true nucleic acids are taken up in a uniformly systematic manner. Each chapter is devoted first to the organic chemistry of the group or individuals of the group, then follow the methods of preparation, specific properties, methods of separation and analytic and synthetic methods. The work of the master mind and hands is obvious throughout the monograph. The structural formulas are presented in a clear manner with Roman numerals for the text references. Naturally, the subject matter is brought up to very recent times, so that the new work on desoxyribosides, methylthiopentosides and the more complex polynucleotides is included. The authors appear to have some doubt as to the certainty of the separation of a 5-methylcytosine from tuberculinic acid. The physicochemical studies by Hammarsten and others on the polynucleotides are presented clearly. The book closes with a chapter on nucleases. Extensive author and subject indexes are included.

Der Mineralbestand des Körpers By Wolfgang Heubner, Professor in Heidelberg. Paper. Price, 8.80 marks. Pp. 94. Berlin: Julius Springer, 1931.

This monograph was written in response to many requests for reprints of a similar compilation written by the author as part of a larger work some years ago. Resumes of this type have a definite value in spite of the unreliability of many of the values found in our periodicals. These are often unreliable because the methods are frequently at fault and also because considerable work is done by those who are not competent to make accurate analyses of this type. The author appears to realize these difficulties, although he does not seem to have attempted to select data with this criticism in mind. No attempt is made to discuss mineral metabolism, but only to present data on the amounts and state of various anions and cations in body fluids, cells and tissues. A brief discussion on the excess base values is included. Calcium and phosphorus naturally are discussed in considerable detail from the normal and pathologic point of view. Rarer inorganic constituents, such as fluorine, bromine, iodine, silicon, copper, manganese, aluminum and arsenic, are also taken up, especially in connection with their distribution in tissues. The author inclines to the view that most of these rarer constituents probably do not have a definite function in the living system, but that they occur there largely through accidental absorption from foods. The teeth, bones, muscle, heart, brain and skin are treated fairly completely.

Neue Wege der Blutdruckmessung Fünfte Abhandlungen über Blutdruck und Puls in den grossen Arterien des Menschen By Heinrich von Recklinghausen Price, 12 marks Pp 289, with 82 illustrations Berlin Julius Springer, 1931

Ostensibly written as an introduction to the use of the "grypotonograph," an apparatus for the oscillographic registration of blood pressure and pulse waves, this book turns out to be a thoroughgoing analysis of the theoretical concepts underlying the measurement of blood pressure, the comparison between direct and indirect methods, the "staircase curve" (pulse tracings obtained during inflation of the manometer cuff from levels below the diastolic to levels above the systolic arterial pressure) and many other interesting problems. Great emphasis is laid on the overpressure produced in the artery above the cuff as the result of artificial obstruction to the pulse wave in the compressed portion of the artery. The form of the individual pulse waves in the graphic record is made use of in determining systolic and diastolic pressures. Comparative data obtained through various methods of blood pressure estimation are critically discussed in the light of the physiology and pathology of the vascular system. Sources of error inherent in the recording apparatus itself are considered from a physical and a mathematical standpoint. Experts will probably not accept some parts of the general theory presented by the author, but serious consideration must be given to evidence submitted by one who has done fundamental research on blood pressure for more than a quarter of a century. This is not a book for the casual reader, though it is written clearly.

Varicose Veins With Special Reference to the Injection Treatment By H O McPheeters, M D, F A C S Third edition Cloth Price, \$4 Pp 285, with 62 illustrations Philadelphia F A Davis Company, 1931

The third edition of this monograph has been thoroughly revised and brought up to date by suitable additions. Most of the faulty references have been corrected although there are still a few misspelled names from the foreign literature. A new chapter has been added on the causes of failure in the injection treatment for varicose veins, containing a critical review of the published recurrences. The author does not condemn high saphenous ligation as strongly as in his previous writings, but still prefers injections into the proximal end of the saphenous trunk. As in previous editions, a whole chapter is devoted to prove the reverse flow of blood in varicose veins.

In the differential diagnostic table on vascular diseases, the data on arterio-venous aneurysms must be challenged. The figures on the oxygen content of venous blood are erroneous. The efficiency of drugs expressed in percentages seems somewhat artificial and arbitrary.

New refinements are added in the chapter on technic. On the whole, the present technic of the author seems unnecessarily complicated. Often heroic quantities of solution are introduced with as many as sixteen injections in one sitting. Such treatment can hardly be called a simple and painless procedure.

The printing and illustrations are excellent. To all who are interested in this field this challenging and stimulating contribution is strongly recommended.

Food Allergy Its Manifestations, Diagnosis and Treatment, with a General Discussion of Bronchial Asthma By Albert H Rowe, M S, M D, Lecturer in Medicine in the University of California Medical School, San Francisco Cloth Price, \$5 Pp 442 Philadelphia Lea & Febiger, 1931

The author of this book has limited his discussion to the manifestations of allergy due to foods and has brought together and summarized the views of most of those who have written on the subject. The extensive bibliography is divided

into two parts, the first being the references related to food allergy, and the second being special references on other phases of allergy

In his voluble enthusiasm on the subject the author explains, on the basis of allergy, many of the common constitutional disorders seen by internists, and he recommends his so-called "elimination diets" in their diagnosis and treatment

The chapter on "elimination diets" includes many helpful recipes and suggestions. Careful and complete preliminary studies and later repeated observations of the patient are properly emphasized. Too frequent repetition of subject matter, too many case reports and the monotonous use of the expressions "in my experience," "in my opinion" and "my elimination diets" make it difficult to hold the reader's interest. Elimination of these faults would add to the enjoyment of the book. This book should be in the library of all students who are interested in dietary problems or who wish to obtain references to this type of literature

Der Wasserversuch als Nierenfunktionsprüfung Eine Zusammenfassung für den Kliniker und praktischen Arzt By Dr Med Ferdinand Lebermann, Facharzt für innere Krankheiten in Würzburg Price, 9 50 marks Pp 148, with 20 illustrations Dresden Theodore Steinkopff, 1932

The author begins with a condensed but fairly complete review of the factors and problems underlying water balance. He then discusses the technic of the dilution and concentration test, the results in normal persons and in patients with the various forms of renal disease and the effects of using diuretics or pituitary extract during the test. There is adequate consideration of extrarenal factors and dilution of the blood as influencing the response to water given by mouth. One gets the impression that the interpretation of a diminished or a delayed excretion of water during the dilution test is so complicated in many instances as to render the procedure valueless. The simplicity of the method is evidently no guarantee for the reliability of the results. Perhaps the most valuable feature of the "Wasserversuch" is its ability to demonstrate latent cardiac edema. After reading through this monograph, one wonders at the remarkable European popularity of the dilution test for renal function. The bibliography will be useful to those who are specially interested.

Approved Laboratory Technic By J A Kolmer and F Boerner Price, \$7 50 Pp 663, with 11 colored plates and 300 illustrations New York D Appleton & Company, 1931

This volume was prepared by the authors for the American Society of Clinical Pathologists. It includes instructions for the examinations of the blood, urine, gastric secretions, exudates and tissue fluids, helpful suggestions for the care and housing of the usual laboratory animals, recipes for mediums, stains and reagent solutions, procedures for bacteriologic technic and the identification of the common pathogenic bacteria and molds, methods for milk and water analyses, technic for the complement fixation and precipitation tests for syphilis, directions for quantitative analyses of the blood and urine, information needed in determining basal metabolism, instructions for preparing sections of tissues, and outlines for certain toxicologic examinations and tests for pregnancy. These directions are adequate, and the tests described include those generally demanded of a large hospital or commercial clinical laboratory. There are no instructions for postmortem technic and other procedures in the morgue. This is anomalous, since clinical pathologists are primarily pathologists in the original sense of the term.

A Diabetic's Own Cook Book By Stella H Lyons Price, \$2 Pp 94 New York Alfred A Knopf, 1932

The foreword of this book is written by Logan Clendenning, M D. He expresses his appreciation of the author as a cook and explains that the little book is in no

sense intended to supplant the physician's instructions to the patient. The diabetic patient will do well to bear this in mind as he reads, for the author says that her real mission is to remove food scales from the layman. Such teaching may be safe for the patient with mild diabetes "on the shady side of forty," as Dr. Clendening writes, but it may also be disastrous to the patient with severe diabetes, be he young or old.

Seventy of the ninety-four pages are filled with recipes and directions for the preparation of food. Ingredients for recipes are measured, but in the end the author ventures to give the food value of single portions of some recipes in fractions of grams of carbohydrate, protein and fat. Patients trained in food values and diet calculation will question the possibility of using "rye bread crumbs or washed bran" without considering the difference in carbohydrate content.

The suggestions offered for the preparation of food are extremely helpful to the patient who lacks imagination, but much of the teaching is unsound.

Manual for the Jewish Diabetic. By William S. Collens, B.S., M.D., Price \$2. Pp. 138. New York: Bloch Publishing Company, 1931.

This is another little book on diabetes. It has as a special appeal a list of diets particularly designed for Jewish diabetic patients. Since the Jews seem to form an undue percentage of the diabetic patients of America, such a book should have a field of usefulness.

We are not convinced that "modern management, simple, easily executed, and rational, brings the diabetic condition rapidly under complete control and restores the person with diabetes to a state of good health." Certainly the text of this book is not as simple to understand as the author seems to consider the disease.

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